# A Convenient Method for Introducing Oxo Group into the β-Position of Cyclic Amines and Its Application to Synthesis of δ-Aminolevulinic Acid

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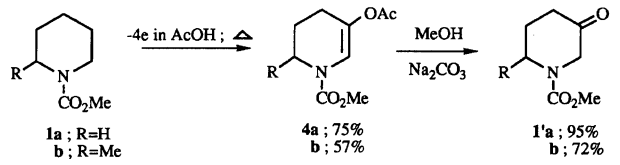
**Synopsis.** Oxo group could be introduced into the β-position of *N*-methoxycarbonylated cyclic amines by utilizing electrochemical oxidation and/or m-chloroperbenzoic acid oxidation, and this method was applied to the preparation of δ-aminolevulinic acid, an intermediate of chlorophyll biosynthesis.

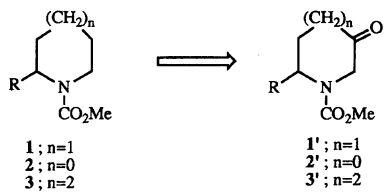
In spite of considerable potentiality of β-oxo cyclic amines as intermediates in the synthesis of nitrogen-containing compounds, their general and convenient synthetic methods are not available.[1] We tried to exploit a method introducing oxo group into the β-position of *N*-protected cyclic amines **1**—**3** (Scheme 1) since it is undoubtedly one of the simplest routes.[2] This paper describes our successful results and an application of one of the products to the synthesis of δ-aminolevulinic acid, an intermediate of chlorophyll biosynthesis showing herbicidal and insecticidal activity.[3] Although several methods have been exploited so far for the preparation of δ-aminolevulinic acid,[4] our method presents a new route for this compound starting from easily available cyclic amine.

Electrochemical and/or peroxy acid oxidations were utilized in our method. Namely, electrochemical oxidation of 1-methoxycarbonylpiperidines **1** in acetic acid followed by heating the resulting solution gave 5-acetoxy-1-methoxycarbonyl-1,2,3,4-tetrahydropyridines **4**. Methanolysis of **4** afforded the desired 1-methoxycarbonyl-3-piperidinones **1′** (Eq. 1).

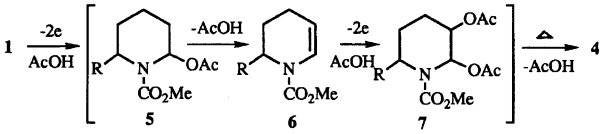



(1)

The formation of **4** from **1** is explained by a four-electrons oxidation mechanism involving α-acetoxylated carbamates **5**, α,β-unsaturated carbamates **6**, and α,β-diacetoxylated carbamates **7** as shown in Scheme 2.[5]



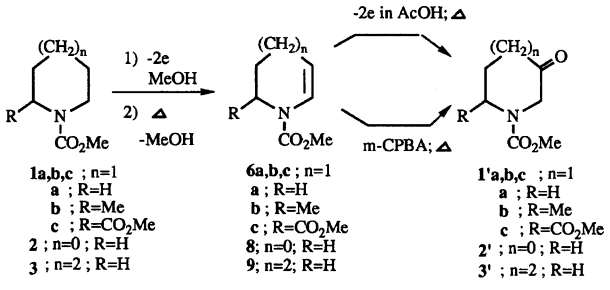

Scheme 1.




Scheme 2.

Since **5**, two-electrons oxidation products of **1**, may be too unstable in acetic acid to afford **6**, further two-electrons-oxidation takes place to give **7** which possess α-acetoxyl group easily removable as acetic acid by heating. Accordingly, **4** can be obtained without carrying out procedures of isolation of **5**—**7**.

On the other hand, in contrast with a successful result of **1a**,**b**, 2-piperidinecarboxylic acid ester **1c**, N-protected pyrrolidine **2** and hexahydroazepine **3** gave poor results because the electrochemical oxidation of **1c** hardly took place in acetic acid, and those of **2** and **3** in acetic acid did not give the corresponding α,β-diacetoxylated products.[6] In aiming to introduce oxo group effectively into β-position of these compounds, we have found a modified method which involves the isolation of α,β-unsaturated carbamates **6**, **8**, and **9** to be oxidized by electrochemical method or peroxy acid (Eq. 2).




(2)

The transformation of **1**, **2** and **3** to the corresponding α,β-unsaturated carbamates **6**, **8**, and **9** could be achieved by our previously reported method.[7] Electrochemical oxidation of thus obtained **6** and **9** in acetic acid, heating the products, and subsequent hydrolysis gave **1′** and **3′**. The yields of products are shown in Table 1.

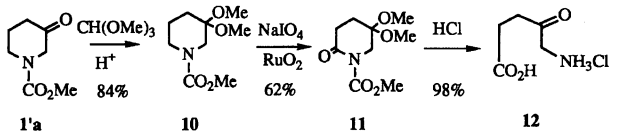
Oxidation of **6**, **8**, and **9** with *m*-chloroperbenzoic acid (*m*-CPBA) in toluene[1b] followed by heating the resulting solution in the presence of a catalytic amount of acid without the isolation of the oxidation products also afforded β-oxo carbamates **1′**, **2′**, and **3′**. The yields are also shown in Table 1.

Table 1. Oxidation of Cyclic Amines

| Run | Starting carbamates | F/mol[a)] | $\alpha,\beta$-Unsaturated carbamates[b)] | $\beta$-Oxo carbamates | |
|---|---|---|---|---|---|
| | | | | electrochemical oxidation[c)] | $m$-CPBA oxidation |
| 1 | **1a** | 2.7 | **6a** (83) | **1'a** (82) | (51) |
| 2 | **1b** | 2.6 | **6b** (63) | **1'b** (65) | (57) |
| 3 | **1c** | 2.5 | **6c** (86) | **1'c** (52) | (51) |
| 4 | **2** | 2.3 | **8** (73) | **2'** (—)[d)] | (38) |
| 5 | **3** | 2.0 | **9** (79) | **3'** (22) | (50) |

a) Electricity passed in methanol to prepare the corresponding $\alpha$-methoxy carbamates. b) Overall yield of electrochemical $\alpha$-methoxylation of carbamates followed by the elimination of methanol. c) 6.0F/mol of electricity was passed. d) Not examined.

One of the products, **1'a**, could be transformed to $\delta$-aminolevulinic acid as follows (Eq. 3). Protection of carbonyl group of **1'a** followed by ruthenium dioxide oxidation gave **11**. Hydrolysis of the product **11** in acetic acid gave $\delta$-aminolevulinic acid hydrochloride **12** in good yield.




(3)

## Experimental

$^1$H NMR spectra were obtained on a 200-MHz Varian Gemini 200 spectrometer with TMS as an internal standard. IR spectra were recorded on a Hitachi 260-10 spectrometer. Mass spectra were obtained on a JEOL IMS-DX 300 instrument. Elemental analyses were determined by the Center for Instrumental Analysis of Kyoto University. Electrochemical oxidation was carried out using DC Power Supply (GP 050-2) of Takasago Seisakusho, Ltd.

**Electrochemical Oxidation of 1-Methoxycarbonylpiperidines 1a,b.** Electrochemical oxidation of **1a,b** was carried out according to the reported method.[7)] Into an undivided cell equipped with platinum electrodes (2 cm×2 cm) was added a solution of **1a,b** (15 mmol) and potassium acetate (3.0 g, 30.6 mmol) in acetic acid (30 mL), and a constant current (0.4 A) was passed for 12 h (12 F mol$^{-1}$). The solution was cooled with running water during the electrolysis and the terminal voltage was 30—40 V. After the electrolysis, the solution was refluxed for 20 min and then the solvent was removed in vacuo to give a syrup. An aqueous solution of $NaHCO_3$ was added to the syrup and extracted with three portions of ether. The extract was dried on $MgSO_4$, and the solvent was removed off in vacuo to give a syrup. The oxidized products, 5-acetoxy-1-methoxycarbonyl-1,2,3,4-tetrahydropyridines **4a,b**, were isolated by column chromatography (silica gel, AcOEt/hexane=1/2).

**4a:** 75% yield; IR (neat) 2950, 1710, 1445, 1360, 1195, 1105, 765 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$=1.85—2.00 (m, 2H), 2.14 (s, 3H), 2.27 (t, $J$=6 Hz, 2H), 3.50—3.65 (m, 2H), 3.75 (s, 3H), 6.79 and 6.90 (two s, 3/5H and 2/5H). Anal. Calcd for $C_9H_{13}NO_4$: C, 54.26; H, 6.58; N, 7.03%. Found: C, 54.45; H, 6.69; N, 6.83%.

**4b:** 57% yield; IR (neat) 2930, 1755, 1700, 1440, 1400, 1340, 1310, 1200, 1170, 1090, 1045, 1015, 1000, 910, 770 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$=1.16 (d, 3H, $J$=6.7 Hz), 1.70—2.20 (m, 3H), 2.14 (s, 3H), 2.34—2.57 (m, 1H), 3.75 (s, 3H), 4.24—4.53 (m, 1H), 6.71 and 6.82 (two s, 3/5H and 2/5H). Anal. Calcd for $C_{10}H_{15}NO_4$: C, 56.30; H, 7.09; N, 6.57%. Found: C, 56.22; H, 7.06; N, 6.73%; MS, $m/z$ 213.09887. Calcd for $C_{10}H_{15}NO_4$: M, 213.10015.

**Hydrolysis of 4a,b.** An aqueous solution of $Na_2CO_3$ (2.070 g, 15 mmol) in water (3 mL) was added into a solution of **4a,b** (9.25 mmol) in methanol (10 mL) and the solution was stirred for 20 min at room temperature. Extraction of organic portion with dichloromethane and purification by column chromatography gave **1'a,b** in 95 and 72% yields, respectively.

**1'a:**[1a)] IR (neat) 2965, 2880, 1700, 1454, 1225, 1120, 965, 772 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$=2.01 (dt, $J$=7 and 8 Hz, 2H), 2.49 (t, $J$=7 Hz, 2H), 3.66 (t, $J$=8 Hz, 2H), 3.73 (s, 3H), 4.06 (s, 2H). Anal. Calcd for $C_7H_{11}NO_3$: C, 53.49; H, 7.05; N, 8.91%. Found: C, 53.72; H, 7.19; N, 8.69%; MS, $m/z$ 157.07390. Calcd for $C_7H_{11}NO_3$: M, 157.07389.

**1'b:** IR (neat) 2990, 1725, 1710, 1695, 1450, 1400, 1350, 1220, 1155, 1105, 1090, 1035, 775 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$=1.26 (d, 3H, $J$=6.6 Hz), 1.52—1.73 (m, 2H), 2.15—2.50 (m, 3H), 3.73 (s, 3H), 4.25—4.54 (m, 2H). Anal. Calcd for $C_8H_{13}NO_3$: C, 56.12; H, 7.65; N, 8.18%. Found: C, 56.02; H, 7.59; N, 8.29%; MS, $m/z$ 171.08887. Calcd for $C_8H_{13}NO_3$: M, 171.08959.

**Formation of $\beta$-Oxo Compounds 1' and 3' by Electrochemical Oxidation Method.** Electrochemical oxidation of **6**[5,7a)] and **9**[5)] in acetic acid was carried out in a similar method to electrochemical oxidation of **1a,b** described above, and the resulted solutions were heated for 20 min after the electrolysis (6 F mol$^{-1}$). The usual working up gave residues which were hydrolyzed under conditions similar to hydrolysis of **4**. The yields of products **1'** and **3'** are shown in Table 1.

**1'c:** IR (neat) 2960, 1738, 1715, 1700, 1450, 1224, 1202, 788 cm$^{-1}$; $^1$H NMR ($CCl_4$) $\delta$=2.11—2.64 (m, 4H), 3.85 (s, 3H), 3.89 (s, 3H), 4.01—5.11 (m, 3H). Anal. Calcd for $C_9H_{13}NO_5$: C, 50.23; H, 6.09: N, 6.51%. Found: C, 50.04; H, 6.13; N, 6.48%.

**3':**[1a)] IR (neat) 2930, 1705, 1465, 1440, 1400, 1320, 1300, 1250, 1215, 1140, 1100, 1070, 995, 945, 915, 880, 770 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$=1.65—1.92 (m, 4H), 2.55 (t, $J$=5.5 Hz, 2H), 3.42 (t, $J$=5 Hz, 1H), 3.49 (t, $J$=5 Hz, 1H), 3.73 (s, 3/2H), 3.78 (s, 3/2H), 4.02 (s, 1H), 4.10 (s, 1H) Found: MS, $m/z$ 171.08860. Calcd for $C_8H_{13}NO_3$: M, 171.08954.

**Oxidation of 6, 8, and 9 with *m*-Chloroperbenzoic Acid.** *m*-Chloroperbenzoic acid (1.1 mmol) was in small portions added into a solution of **6**, **8**,[7a] and **9** (1 mmol) in toluene (5 mL) at room temperature, and the solution was stirred for 10 min. Then, a catalytic amount of *p*-toluenesulfonic acid was added and the resulting solution was refluxed for 15 min. After cooled, the solution was washed with an aqueous $NaHCO_3$ and extracted with dichloromethane. The usual working up followed by subjection of the residue on column chromatography gave **1′**, **2′** and **3′** in the yields shown in Table 1.

**2′:**[8] mp 62°; IR (neat) 2960, 2900, 1750, 1705, 1460, 1390, 1160, 770 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$=2.62 (t, $J$=8 Hz, 2H), 3.84 (t, $J$=8 Hz, 2H), 3.76 (s, 3H), 3.80 (s, 2H); MS, $m/z$ 143.05727. Calcd for $C_6H_9NO_3$; M, 143.05824.

**Protection of 1′a.** Into a solution of **1′a** (0.630 g, 4.0 mmol) in trimethyl orthoformate (5 mL) was added a catalytic amount of *p*-toluenesulfonic acid, and the solution was stirred for 30 min. After addition of an aqueous $NaHCO_3$ into the solution, the organic portion was extracted with dichloromethane (20 mL×3) and the extract was dried on $MgSO_4$. Evaporation of the filtrate gave a syrup, which was subjected on column chromatography (AcOEt/hexane= 1/1) to afford **10** (0.685 g, 3.37 mmol; 84% yield).

**10:** IR (neat) 2940, 1700, 1460, 1240, 1180, 1105, 1055, 860, 775 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$=1.55—1.70 (m, 2H), 1.70—1.81 (m, 2H), 3.22 (s, 6H), 3.45—3.53 (m, 4H), 3.71 (s, 3H); MS, Found: $m/z$ 203.11424. Calcd for $C_9H_{17}NO_4$: M, 203.11575. MS, $m/z$ 172, 140, 114, 102, 101 (base).

**Oxidation of 10 with Ruthenium Dioxide.** This oxidation was carried out according to the reported procedure.[9] A solution of **10** (406 mg, 2 mmol) in AcOEt (10 mL) was added into a mixture of 40 mg (0.3 mmol) of ruthenium dioxide and an aqueous solution of $NaIO_4$ (2.14 g, 10 mmol) in 20 mL of water, and the resulting solution was stirred at room temperature for 18 h. The organic portion was seperated, the aqueous phase was extracted with AcOEt (20 mL×3), and 2-propanol (3 mL) was added into the combined organic solution to destroy ruthenium tetraoxide. The solution was stirred for 2 h at room temperature, the black precipitate was filtered off, and organic portion was dried on $MgSO_4$. The removal of the drying agent and evaporation of the solvent gave a syrup, which was subjected to column chromatography (silica gel, AcOEt/hexane=1/1) to afford **11** (270 mg, 1.24 mmol).

**11:** 62% yield; IR (neat) 2920, 1720, 1440, 1300, 1270, 1130, 1080, 1050 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$=2.02 (t, $J$=6 Hz, 2H), 2.59 (t, $J$=6 Hz, 2H), 3.25 (s, 6H), 3.83 (s, 2H), 3.88 (s, 3H); Found: $m/z$ 217.09564. Calcd for $C_9H_{15}NO_5$: M, 217.09501. MS $m/z$ 196, 154, 128, 102, 101 (base).

**Hydrolysis of 11 to δ-Aminolevulinic Acid Hydrochloride 12.** A solution of **11** (132 mg, 0.61 mmol) in 7 M HCl (5 mL) and ethanol (1 mL) was refluxed for 12 h, and then the solvent was removed in vacuo to give a crude δ-aminolevulinic acid hydrochloride (101 mg, 0.60 mmol, 98% yield). Recrystallization from methanol and ethyl acetate yielded a pure **12** (79.0 mg, 0.47 mmol, 77% yield), of which spectroscopic and physical data (mp 144—147 °C) were identical with those of authentic sample.[10]

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