Supporting Information

Unique Oxidation Reaction of Amides with Pyridine *N*-oxide Catalyzed by Ruthenium Porphyrin

– Direct Oxidative Conversion of *N*-Acyl-L-proline to *N*-Acyl-L-glutamate

Rina Ito, Naoki Umezawa, Tsunehiko Higuchi*

*Graduate School of Pharmaceutical Sciences, Nagoya City University,
3-1 Tanabe-dori, Mizuho-ku, Nagoya, Japan*

Table S-1. Oxidation of 4a by Ru^{IV} Tetraarylporphyrin Dichloride / 2,6-Substituted Pyridine *N*-Oxide System

entry	oxidant	Ru porphyrin	isolated yield
1	R = Cl	Ru(TMP)Cl ₂	89 %
2	R = Me	Ru(TMP)Cl ₂	60 %
3	R = Cl	Ru(TPP)Cl ₂	54 %

Reaction conditions: substrate (0.16 M), Ru-porphyrin (0.6 mol%), and oxidant (0.48 M) were stirred in benzene at 40 °C under Ar overnight. Yields are based on the substrate used.

Table S-2. Oxidation of Aldehydes

entry	substrate	product, isolated yield
1	12a	12b , 93 %
2 ^a	13a	13b , 87 %
3	14a	14b , 74 % 14c , 11 %
4	3c	3b , 66 %

Reaction conditions: substrate (0.16 M), Ru(TMP)Cl₂ (0.6 mol%), and 2,6-dichloropyridine *N*-oxide (0.19 M) were stirred in benzene at 40 °C under Ar overnight, unless otherwise noted. Yields are based on the substrate used. ^a The reaction was carried out for 5 h.

Figure S-1 NOE Experiments for Compound 1a at -30°C and 24°C in CDCl_3

Figure S-2. Time Course of N-Benzoylpyrrolidine (1a) Oxidation

Experimental Section

General Methods.

Proton nuclear magnetic resonance (^1H NMR) spectra were recorded on a JEOL JNM GSX-400 (400 MHz) pulse Fourier transform NMR spectrometer. Chemical shifts are expressed in parts per million (ppm) downfield from internal tetramethylsilane ($\delta = 0$) and coupling constants are reported as Hertz (Hz). Splitting patterns are indicated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Column chromatography was carried out using BW-200 (Fuji Silysia, Japan), and thin layer chromatography (TLC) was performed on Merck precoated plates (silica gel 60 F₂₅₄, 0.25 mm). FAB mass spectra were recorded on a JEOL JMS-LCmate spectrometer. Benzene and CH_2Cl_2 were freshly distilled over CaH_2 . Ether was freshly distilled from Na.

Preparation of *N*-acyl amino acids by the oxidation of *N*-acyl cyclic amines with 2,6-dichloropyridine *N*-oxide / Ru porphyrin system.

A typical procedure for *N*-benzoyl amino acid preparation in Table 1, Entry 1-3 is as follows. A solution of *N*-benzoyl cyclic amine (0.80 mmol), 2,6-dichloropyridine *N*-oxide (1.6 mmol, 2 eq.), and $\text{Ru}(\text{TMP})\text{Cl}_2$ (5mg, $5\mu\text{mol}$) in benzene (5 mL) was stirred overnight under Ar at 40 °C. Benzene was evaporated under reduced pressure, then the residue was chromatographed on silica gel (eluent: CH_2Cl_2 -AcOEt) to afford *N*-benzoyl amino acid.

4-Benzoylaminobutanoic acid (1b**)**

^1H NMR (CDCl_3/TMS) 7.77 (d, 2H, $J=7.2$ Hz), 7.45 (m, 3H), 6.55 (bs, 1H), 3.55 (q, 2H, $J=6.4$ Hz), 2.49 (t, 2H, $J=6.8$ Hz), 1.98 (m, 2H); MS (FAB) 208 ($M+1$)

γ -Benzoylamino- γ -lactone (1c**)**

^1H NMR (CDCl_3/TMS) 7.80 (d, 2H $J=7.6$ Hz), 7.53 (m, 3H), 6.69 (bs, 1H), 6.41 (bs, 1H), 2.70 (m, 3H), 2.15 (m, 1H); MS (FAB) 206 ($M+1$)

***N*-Benzoylpyrrolidone (**1d**)**

^1H NMR (CDCl_3/TMS) 7.47 (m, 5H), 3.97 (t, 2H, $J=7.0$ Hz), 2.62 (t, 2H, $J=8.0$ Hz), 2.16 (m, 2H); MS (FAB) 190 ($M+1$)

5-Benzoylaminopentanoic acid (2b**)**

¹H NMR (CDCl₃/TMS) 7.78 (d, 2H, J=7.6 Hz), 7.50 (m, 3H), 6.29 (bs, 1H), 3.49 (m, 2H), 2.46 (m, 2H), 1.74 (m, 4H); MS (FAB) 222 (M+1)

6-Benzoylaminohexanoic acid (**3b**)

¹H NMR (CDCl₃/TMS) 7.77 (m, 2H), 7.50 (m, 3H), 6.19 (bs, 1H), 3.48 (m, 2H), 2.39 (t, 2H, J=7.2 Hz), 1.68 (m, 4H), 1.46 (m, 2H); MS (FAB) 236 (M+1)

6-Benzoylaminohexanal (**3c**)

¹H NMR (CDCl₃/TMS) 9.78 (s, 1H), 7.76 (m, 2H), 7.46 (m, 3H), 6.17 (bs, 1H), 3.48 (m, 2H), 2.48 (m, 2H), 1.68 (m, 4H), 1.43 (m, 2H); MS (FAB) 220 (M+1)

A typical procedure for *N*-acyl amino acid preparation in Table 1, Entry 4-5 is as follows. A solution of *N*-acyl cyclic amine (0.80 mmol), 2,6-dichloropyridine *N*-oxide (2.1 mmol, 2.5 eq.), and Ru(TMP)Cl₂ (5mg, 5μmol) in benzene (5 mL) was stirred overnight under Ar at 40 °C. Benzene was evaporated under reduced pressure, then the residue was chromatographed on silica gel (eluent: CH₂Cl₂-AcOEt) to afford *N*-acyl amino acid.

6-Benzoylamino-5-methylpentanoic acid (**4b**)

¹H NMR (CDCl₃/TMS) 7.76 (d, 2H, J=7.2 Hz), 7.58 (m, 3H), 5.99 (bd, 1H), 4.23 (m, 1H), 2.43 (m, 2H), 1.69 (m, 4H), 1.26 (d, 3H, J=6.4 Hz); MS (FAB) 236 (M+1)

6-Boc-amino-5-methylpentanoic acid (**5b**)

¹H NMR (CDCl₃/TMS) 4.35 (bs, 1H), 3.67 (br, 2H), 2.38 (m, 2H), 1.68 (m, 2H), 1.44 (s, 9H), 1.13 (d, 3H, J=6.4 Hz); MS (FAB) 232 (M+1)

Preparation of *N*-benzoylglutamic acids derivatives by the oxidation of *N*-benzoylproline derivatives with this system.

A typical procedure for *N*-benzoylglutamic acid derivative preparation in Table 2 is as follows. A solution of *N*-benzoylproline derivative (0.80 mmol), 2,6-dichloropyridine *N*-oxide (2.1 mmol, 2.5 eq.), and Ru(TMP)Cl₂ (5mg, 5μmol) in benzene (5 mL) was stirred overnight under Ar at 40 °C. Benzene was evaporated under reduced pressure, then the residue was chromatographed on silica gel (eluent: AcOEt-EtOH) to afford *N*-benzoylglutamic acid derivative.

N-Benzoyl-L-glutamic acid (**6b**)

¹H NMR (DMSO) 8.59 (d, 1H, J=7.6 Hz), 7.86 (d, 2H, J=7.6 Hz), 7.49 (m, 3H), 4.40 (br, 1H), 2.35 (t, 2H, J=7.6 Hz), 2.01 (m, 2H); MS (FAB) 252 (M+1)

Bz-L-Glu-L-Ala-OEt (**7b**)

¹H NMR (CDCl₃/TMS) 7.83 (d, 2H, J=7.2 Hz), 7.46 (m, 3H), 4.88 (m, 1H), 4.54 (m, 1H), 4.20 (q, 2H, J=7.2 Hz), 2.62 (m, 2H), 2.26 (m, 2H), 2.11 (m, 1H), 1.43 (d, 2H, J=7.2 Hz), 1.29 (t, 3H, J=7.2 Hz); MS (FAB) 351 (M+1)

Bz-L-Glu-L-Val-OMe (**8b**)

¹H NMR (DMSO) 12 (bs, 1H), 8.50 (br, 1H), 8.18 (d, 1H, J=7.6 Hz), 7.86 (m, 2H), 7.47 (m, 3H), 4.52 (m, 1H), 4.17 (t, 1H, J=7.0 Hz), 3.62 (s, 3H), 2.32 (m, 2H), 2.00 (m, 2H), 0.88 (m, 6H); MS (FAB) 365 (M+1); E. A. C₁₉H₂₆N₂O₆: Calcd. C: 59.33, H: 6.64, N: 7.69. Found. C: 59.09, H: 6.70, N: 7.82; m. p. 58 °C

Preparation of *N*-Benzoyl[2,2-*d*₂]pyrrolidine (1e**)**

To LiAlD₄ (90 mg, 2.2 mmol) in 30 mL of ether was added 2-pyrrolidone (0.27 mL, 3.6 mmol) under Ar. The solution was warmed to reflux for 3 h. Following cooling to rt, ether (12mL), Na₂SO₄•10H₂O, brine, and Na₂SO₄ was added and the colorless precipitate was filtered. The solvent was concentrated under reduced pressure. The residue was dissolved in CH₂Cl₂ (24 mL), and DMAP (580 mg, 4.8 mmol) was added under Ar. The mixture was cooled to 0 °C, benzoyl chloride (0.55 mL, 4.7 mmol) was added. Stirring was continued for 1 h at 0 °C and for 15 h at rt. The resulting solution was washed with water (3 x 30 mL) and brine (30 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The product was purified by column chromatography (eluent: CH₂Cl₂, then CH₂Cl₂/AcOEt, 1:1, then AcOEt) to give colorless oil (93 mg, 15 % yield).

¹H NMR (CDCl₃/TMS) 7.52 (m, 2H), 7.40 (m, 3H), 3.65 (t, 1H, J=6.8 Hz), 3.42 (t, 1H, J=6.8Hz), 1.96 (m, 2H), 1.87 (m, 2H); MS (FAB) 178(M+1)

Oxidation of *N*-Benzoyl[2,2-*d*₂]pyrrolidine with this system

A solution of *N*-Benzoyl[2,2-*d*₂]pyrrolidine (60 mg, 0.34 mmol), 2,6-dichloropyridine *N*-oxide (110 mg, 0.68 mmol), and Ru(TMP)Cl₂ (2mg, 2μmol) in benzene (2 mL) was stirred

overnight under Ar at 40 °C. Benzene was evaporated under reduced pressure, then the residue was chromatographed on silica gel (eluent: CH₂Cl₂-AcOEt).

1f:

¹H NMR (CDCl₃/TMS) 7.78 (d, 2H, J=7.6 Hz), 7.52 (t, 1H, J=7.3 Hz), 7.44 (dd, 2H, J=7.6 Hz, 7.3 Hz), 6.49 (bs, 1H), 2.50 (t, 2H, J=6.8 Hz), 1.97 (t, 2H, J=6.8 Hz); MS (FAB) 210 (M+1)

1g:

¹H NMR (CDCl₃/TMS) 7.80 (d, 2H, J=7.6 Hz), 7.55 (m, 3H), 6.73 (bs, 1H), 2.71 (m, 3H), 2.20 (m, 1H); MS (FAB) 207 (M+1)

1h:

¹H NMR (CDCl₃/TMS) 7.61 (d, 2H, J=7.3 Hz), 7.52 (dd, 1H, J=7.3 Hz, 7.6 Hz), 7.41 (t, 2H, J=7.6 Hz), 2.62 (t, 2H, J= 8.1 Hz), 2.14 (m, 2H); MS (FAB) 192 (M+1)

Selectivity in the C-N bond cleavage

It has been reported that an equal population of *cis* and *trans* forms in the planar configuration is present in the case of **4a**, the amide C-N bond can rotate at -10 °C or higher, and the methyl group is in axial configuration (ref. R. A. Johnson *J. Org. Chem.* 1968, 33, 3627). In the *trans* form, attack at the hydrogen at the 2 position would be prevented by electrostatic repulsion between the carbonyl oxo and oxo-Ru species, since the equatorial C-H (2) bond and the neighboring C=O bond are close and parallel. In the *cis* form, the hydrogen at the 2-position is sterically too hindered to react with oxo-Ru active species. On the other hand, oxo-Ru would be able to attack the axial hydrogen at the 6 position which can escape from the repulsion and the hindrance.

Rotation of the Amide Bond in Compound **1a**

NOE experiments on *N*-benzoylpyrrolidine **1a** were performed in order to clarify whether the amide bond rotates at the reaction temperature (Figure S-1). At -30 °C, NOE was observed at the aromatic region and not at the δ 3.65 peaks on irradiation of the peaks at δ 3.43 (Chart (b), and NOE at δ 3.43 was not observed by the irradiation of the peaks at δ 3.65 (Chart (c)). The results indicate that the amide bond does not rotate at -30 °C. The peaks at δ 3.43 represent *cis*- α -hydrogens and δ 3.65 peaks represent *trans*- α -hydrogens as shown below. On the other hand, NOE at δ 3.65 was observed on irradiation of the peaks at δ 3.43 and NOE at δ 3.43 was also observed on irradiation of the peaks at δ 3.65 at 24 °C (Chart (e) and (f)). These results indicate that the amide bond rotates at 24 °C.

N-Benzoyl[2,2- d_2]pyrrolidine (**1e**) also has peaks at δ 3.43 and δ 3.65, each with an integral value of 1H. Therefore, the amide bond of **1e** also rotates at room temperature, ensuring equivalency. This result supports the view that our method for determining k_H/k_D is appropriate.

Determination of k_H/k_D value

The k_H/k_D value is determined by the ratio of the first-step products (**A**)/(**B**). All of the formed intermediate **A** is converted into **1f**, **1g** and **1h**. Therefore, the sum of **1f**, **1g** and **1h** should represent the sum of the formed **A**, and the sum of the formed intermediate **B** can be

determined in the same manner. Thus, the k_H/k_D value can be determined by calculating $(\mathbf{1f} + \mathbf{1g} + \mathbf{1h}) / (\mathbf{1b} + \mathbf{1c} + \mathbf{1d})$. The yields shown below are the values that were derived from one of two experiments.

Time Course of Oxidation Reaction

A solution of *N*-benzoylpyrrolidine (119 mg, 0.68 mmol), phenanthrene (internal standard; 59 mg, 0.33 mmol), 2,6-dichloropyridine *N*-oxide (268 mg, 1.6 mmol), and Ru(TMP)Cl₂ (3.8 mg, 4.0 μmol, 0.6 mol%) in C₆D₆ (4.0 mL) was stirred under Ar at 40 °C. After the appropriate reaction time, 0.20 mL of the reaction mixture was taken and diluted with CDCl₃ containing 0.16 % pyridine (0.50 mL). The yield of each compound was determined by ¹H NMR, respectively. The peaks used for the yield calculation were as follows:

Phenanthrene: 8.60 (d, 2H, J=7.6 Hz)

Intermediate 1: 9.57 (s, 1H, -CHO)

Intermediate 2: 5.73 (br, 1H, -N-CH-C-), 5.08 (bs, 1H, -OH)

Oxidation of aldehydes with this system

A typical procedure of aldehyde oxidation in Table S-2 is as follows. A solution of aldehyde (0.50 mmol), 2,6-dichloropyridine *N*-oxide (97 mg, 0.60 mmol), and Ru(TMP)Cl₂ (3mg, 3μmol) in benzene (3 mL) was stirred overnight under Ar at 40 °C. Benzene was evaporated under reduced pressure, then the residue was chromatographed on silica gel (eluent: CH₂Cl₂-AcOEt) to afford carboxylic acid.

Benzoic acid (**12b**)

¹H NMR (CDCl₃/TMS) 8.11 (d, 2H, J=7.6 Hz), 7.62 (t, 1H, J=7.6 Hz), 7.48 (t, 2H, J=7.6 Hz); MS (FAB) 123 (M+1)

Hexanoic acid (**13b**)

¹H NMR (DMSO) 12 (bs, 1H), 2.17 (t, 2H, J=7.4 Hz), 1.48 (m, 2H), 1.25 (m, 4H), 0.85 (t, 3H, J=6.8 Hz)

2-Phenylpropanoic acid (**14b**)

¹H NMR (DMSO) 12.3 (bs, 1H), 7.26 (m, 5H), 3.65 (q, 1H, J=7.2 Hz), 1.34 (d, 3H, J=7.2 Hz)

Acetophenone (**14c**)

¹H NMR (CDCl₃/TMS) 7.97 (d, 2H, J=7.2 Hz), 7.53 (m, 3H), 2.62 (s, 3H)

Oxidation of lactams with this system

A typical procedure of lactam oxidation in Table 3 is as follows. A solution of lactam (0.50 mmol), 2,6-dichloropyridine *N*-oxide (200 mg, 1.2 mmol), and Ru(TMP)Cl₂ (3mg, 3μmol) in benzene (3 mL) was stirred overnight under Ar at 40 °C. Benzene was evaporated under reduced pressure, then the residue was chromatographed on silica gel (eluent: CH₂Cl₂-AcOEt) to afford imides or ring-opened products.

N-Methylsuccinimide (**9b**)

¹H NMR (CDCl₃/TMS) 3.00 (s, 3H), 2.72 (s, 4H); MS (FAB) 113 (M⁺)

N-Methylglutarimide (**10b**)

¹H NMR (CDCl₃/TMS) 3.15 (s, 3H), 2.66 (t, 4H, J=6.6 Hz), 1.95 (m, 2H); MS (FAB) 128(M+1)

N-Methylaminocarbonyl pentanal (**11b**)

¹H NMR (CDCl₃/TMS) 9.40 (s, 1H), 5.00 (bs, 1H), 3.79 (t, 2H, J=4.5 Hz), 2.82 (d, 3H, J=4.6 Hz), 2.68 (m, 2H), 2.39 (m, 1H), 2.21 (m, 1H), 1.79 (m, 1H), 1.69 (m, 1H)