Aerobic, Organocatalytic, and Chemoselective Method for Baeyer-Villiger Oxidation

Yasushi Imada,* Hiroki Iida, Shun-Ichi Murahashi,* and Takeshi Naota*

Department of Chemistry, Graduate School of Engineering Science, Osaka University, and PRESTO, Japan Science and Technology Agency (JST)
1-3, Machikaneyama, Toyonaka, Osaka 560-8531, Japan

General. NMR spectra were obtained on a JEOL JNM-GSX-270 NMR spectrometer (\(^1\)H, 270 MHz; \(^{13}\)C, 68 MHz) and a Varian Unity-Inova 500 NMR spectrometer (\(^1\)H, 500 MHz; \(^{13}\)C, 126 MHz). UV-vis spectra were recorded on a Shimadzu MultiSpec-1500 spectrophotometer. Mass spectra were obtained on a JEOL JMS-DX303HF mass spectrometer. IR spectra were recorded on a Shimadzu FTIR-4100 spectrometer and a Bruker EQUINOX 55. All melting point were measured on a BÜCHI Melting Point B-545.

Materials. Riboflavin, methyl \(p\)-tolyl sulfide, diethylene glycol diethyl ether, \(\text{CH}_3\text{I}\), acetaldehyde, 80% \(m\text{CPBA}\), 37% aqueous formaldehyde solution, 30% aqueous \(\text{H}_2\text{O}_2\) solution, 28% aqueous ammonia solution, 70% aqueous \(\text{HClO}_4\) solution, \(\text{NaBH}_3\text{CN}\), \(\text{Na}_2\text{S}_2\text{O}_4\), \(\text{NaNO}_2\), \(\text{NaClO}_4\), \(\text{K}_2\text{CO}_3\), and zinc dust were commercially available and used without further purification. Bicyclo[3.2.0]hept-2-en-6-one and cyclooctene were commercially available and distilled prior to use. 3-Substituted cyclobutanones\(^1\) and 3-hydroxybicyclo[3.2.0]heptan-6-one\(^2\) were prepared according to the literature procedure.

Preparation of 3-Methyl-2',4':3',5'-di-\(O\)-methylenerriboflavin. A mixture of riboflavin (376 mg, 1.0 mmol), conc. HCl (600 \(\mu\)L), and 37% aqueous formaldehyde solution (900 \(\mu\)L) was refluxed in a water-bath at 60 °C for 48 h. The resulting mixture was evaporated under reduced
pressure at 80 °C. K$_2$CO$_3$ (1.38 g, 10 mmol), DMF (100 mL), and CH$_3$I (0.620 mL, 10 mmol) was added to the resulting crude O-protected riboflavin, and the mixture was stirred at room temperature for 24 h. After extraction with CHCl$_3$, the combined organic layers were dried over MgSO$_4$ and evaporated under reduced pressure. The crude product was purified by column chromatography on alumina to give 3-methyl-2’,4’:3’,5’-di-O-methylene riboflavin (153 mg, 37%) as a yellow powder: mp >300 °C; $^1$H NMR (CDCl$_3$, 500 MHz) δ 2.44 (s, 3 H, ArCH$_3$), 2.55 (s, 3 H, ArCH$_3$), 3.52 (s, 3 H, NC$_3$H$_3$), 3.54-3.61 (m, 3 H), 4.17-4.19 (m, 1 H), 4.26-4.30 (m, 1 H), 4.62 (d, $J = 6.4$ Hz, 1 H, OCH$_2$O), 4.69 (d, $J = 6.4$ Hz, 1 H, OCH$_2$O), 4.91-4.92 (m, 2 H), 5.05 (d, $J = 6.2$ Hz, 1 H, OCH$_2$O), 5.10 (br, 1 H), 7.56 (s, 1 H, ArH), 8.06 (s, 1 H, ArH); $^{13}$C NMR (CDCl$_3$, 126 MHz) δ 19.4, 21.6, 28.7, 45.2, 68.2, 72.8, 75.0, 77.1, 93.5, 94.1, 116.0, 131.8, 132.6, 134.8, 135.6, 136.5, 147.4, 149.2, 155.7, 160.0; IR (KBr) 1712 (C=O, m), 1658 (C=O, s), 1584 (m), 1547 (s), 1350 (w), 1277 (w), 1237 (m), 1078 (m), 1053 (w), 1014 (w), 990 (m), 980 (m) cm$^{-1}$; HRMS (FAB) calcd for C$_{20}$H$_{23}$O$_6$N$_4$ (M + H$^+$) 415.1618, found 415.1629.

**One-Pot Synthesis of 5-Ethyl-3-methyl-2’,4’:3’,5’-di-O-methyleneriboflavinium Perchlorate (DMRFlEt’$^+$ClO$_4$).** Acetaldehyde (2.20 g, 50 mmol) was added to a mixture of 3-methyl-2’,4’:3’,5’-di-O-methylene riboflavin (207 mg, 0.50 mmol), NaBH$_3$CN (314 mg, 5.0 mmol), Na$_2$S$_2$O$_4$ (348 mg, 2 mmol), acetic acid (150 µL), and dry DMF (12 mL) under argon, and the mixture was stirred for 2 h at 60 °C. After extraction of the resulting yellow mixture with CHCl$_3$ (100 mL), the organic layer was washed with brine (30 mL) and evaporated under reduced pressure to give the yellow residue. A mixture of Na$_2$S$_2$O$_4$, EtOH (2.5 mL), and 10% aqueous ammonia (2.5 mL) was added to the residue, and 4 M aqueous HClO$_4$ solution (6.0 mL), NaNO$_2$ (138 mg, 2.0 mmol), and NaClO$_4$ (306 mg, 2.5 mmol) was added successively at 0 °C. After the mixture was stirred at room temperature, the resulting purple precipitate was collected by filtration, washed successively with water (5 mL x 2), MeOH (5 mL x 2), ether (5 mL x 3), and CHCl$_3$ (5 mL x 3), and dried under reduced pressure to give 5-ethyl-3-methyl-2’,4’:3’,5’-di-O-methyleneriboflavinium perchlorate (172 mg, 63%) as a purple powder: mp 206-208 °C; UV (CH$_3$CN) $\lambda_{\text{max}}$ 418 nm ($\varepsilon = 8420$ M$^{-1}$ cm$^{-1}$), 559 nm ($\varepsilon = 6590$ M$^{-1}$ cm$^{-1}$).
cm⁻¹); IR (KBr) 1710 (C=O, w), 1650 (C=O, m), 1600 (w), 1560 (w), 1500 (Cl–O, s) cm⁻¹; HRMS (FAB) calcd for C₂₂H₂₈O₆N₄ (M –ClO₄⁻ + H⁺) 444.2009, found 444.1976.

**General Procedure for Baeyer-Villiger Oxidation of Cyclobutanones.** A mixture of DMRFlEt⁺ClO₄⁻ (5.4 mg, 0.010 mmol), cyclobutanone (0.50 mmol), and zinc dust (49.0 mg, 0.75 mmol) in a mixed solvent of acetonitrile, ethyl acetate, and water (8:1:1, v/v, 0.5 mL) was stirred under molecular oxygen filled in a gas balloon at 60 ℃. After stirring for 7 h, the reaction was quenched by adding saturated Na₂SO₃ aqueous solution (5 mL), and the mixture was extracted with ethyl acetate (5 mL x 5). The combined extracts were dried over Na₂SO₄ and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel to afford the corresponding γ-butyrolactone. The results are summarized in Table 1 of the text.

3-(2-Naphthyl)-γ-butyrolactone: mp 115-116 ℃; ¹H NMR (CDCl₃, 500 MHz) δ 2.79 (dd, J = 8.7, 17.2 Hz, 1 H, -C(O)CH₃), 3.00 (dd, J = 8.7, 17.7 Hz, 1 H, -C(O)CH₂-), 3.92-3.99 (m, 1 H, ArCH), 4.38 (dd, J = 7.7, 9.2 Hz, 1 H, -OCH₂-), 4.74 (dd, J = 7.7, 9.2 Hz, 1 H, -OCH₂-), 7.34-7.40 (m, 2 H, ArH), 7.48-7.53 (m, 2 H, ArH), 7.67 (dd, J = 0.5, 1.5 Hz, 1 H, ArH), 7.80-7.85 (m, 2 H, ArH), 7.87 (d, J = 9.0 Hz, 1 H, ArH); ¹³C NMR (CDCl₃, 126 MHz) δ 35.6, 41.2, 73.9, 124.5, 125.5, 126.2, 126.6, 127.6, 127.7, 129.1, 132.6, 133.3, 136.7, 176.4; IR (KBr) 3054 (w), 2968 (w), 2903 (w), 1762 (s), 1598 (s), 1507 (s), 1483 (s), 1418 (s), 1360 (s), 1160 (s), 1009 (s), 861 (s), 832 (s), 750 (s) cm⁻¹; HRMS (EI) calcd for C₁₄H₁₂O₂ (M⁺) 212.0837, found 212.0818.

3-Phenyl-γ-butyrolactone: mp 115-116 ℃; ¹H NMR (CDCl₃, 500 MHz) δ 2.68 (dd, J = 9.2, 17.4 Hz, 1 H, -C(O)CH₂-), 2.93 (dd, J = 8.7, 17.4 Hz, 1 H, -C(O)CH₃), 3.76-3.83 (m, 1 H, ArCH), 4.27 (dd, J = 8.0, 9.2 Hz, 1 H, -OCH₂-), 4.67 (dd, J = 7.9, 9.1 Hz, 1 H, -OCH₂-), 7.23-7.25 (m, 2 H, ArH), 7.29-7.32 (m, 1 H, ArH), 7.36-7.39 (m, 2 H, ArH); ¹³C NMR (CDCl₃, 126 MHz) δ 35.6, 41.1, 74.0, 126.7, 127.7, 129.1, 139.4, 176.3; MS (CI) m/z 163 (M + H⁺).

3-(p-Fluorophenyl)-γ-butyrolactone: mp 69 ℃; ¹H NMR (CDCl₃, 500 MHz) δ 2.64 (dd, J =
8.9, 17.6 Hz, 1 H, -C(O)CHH-), 2.93 (dd, J = 8.8, 17.6 Hz, 1 H, -C(O)CHH-, 3.76-3.82 (m, 1 H, ArCH), 4.24 (dd, J = 7.8, 9.2 Hz, 1 H, -OCHH-), 4.66 (dd, J = 7.8, 9.2 Hz, 1 H, -OCHH-), 7.04-7.09 (m, 2 H, ArH), 7.20-7.24 (m, 2 H, ArH); 13C NMR (CDCl$_3$, 126 MHz) δ 35.7, 40.4, 73.9, 116.0 (d, J = 21.6 Hz), 128.2 (d, J = 8.2 Hz), 135.2 (d, J = 2.9 Hz), 162.1 (d, J = 247 Hz), 176.0; IR (KBr) 3531 (w), 3069 (m), 2965 (m), 2908 (m), 1766 (C=O, s), 1602 (m), 1515 (s), 1481 (m), 1433 (m), 1220 (m), 1166 (s), 1013 (s), 843 (s), 824 (m), 802 (m), 542 (s) cm$^{-1}$; HRMS (EI) calcd for C$_{10}$H$_9$O$_2$F (M$^+$) 180.0587, found 180.0584.

3-(p-Chlorophenyl)-γ-butyrolactone: 1H NMR (CDCl$_3$, 500 MHz) δ 2.64 (dd, J = 9.0, 17.5 Hz, 1 H, -C(O)CHH-), 2.93 (dd, J = 9.0, 17.5 Hz, 1 H, -C(O)CHH-), 3.74-3.81 (m, 1 H, ArC), 4.24 (dd, J = 7.7, 9.2 Hz, 1 H, -OCHH-), 4.66 (dd, J = 8.0, 9.0 Hz, 1 H, -OCHH-), 7.16-7.19 (m, 2 H, ArH), 7.27-7.36 (m, 2 H, ArH); 13C NMR (CDCl$_3$, 126 MHz) δ 35.6, 40.5, 73.7, 128.0, 129.3, 133.5, 137.9, 175.9; HRMS (EI) calcd for C$_{10}$H$_9$O$_2$F (M$^+$) 196.0291, found 196.0268.

3-Octylbutyrolactone: 1H NMR (CDCl$_3$, 500 MHz) δ 0.88 (t, J = 7.0 Hz, 3 H, CH$_3$), 1.22-1.33 (m, 12 H, -CH$_2$-), 1.43-1.49 (m, 2 H, -CHCH$_2$-), 2.18 (dd, J = 8.0, 17.0 Hz, 1 H, -C(O)CHH-), 2.51-2.57 (m, 1 H, CH), 2.62 (dd, J = 8.5, 17.0 Hz, 1 H, -C(O)CHH-), 3.92 (dd, J = 7.0, 9.0 Hz, 1 H, -OCHH-), 4.42 (dd, J = 7.5, 9.0 Hz, 1 H, -OCHH-); 13C NMR (CDCl$_3$, 126 MHz) δ 14.0, 22.6, 27.4, 29.2, 29.4, 29.5, 31.8, 33.1, 34.5, 35.7, 73.4, 177.2; MS (CI) m/z 199 (M + H$^+$).

Oxidation of 3-Hydroxybicyclo[3.2.0]heptan-6-one.

7-Hydroxy-2-oxabicyclo[3.3.0]octa-3-one (major isomer): 1H NMR (CDCl$_3$, 500 MHz) δ 1.83-2.28 (m, 5 H), 2.57 (dd, J = 2.6, 18.5 Hz, 1 H, -C(O)CHH-), 2.85 (dd, J = 11.2, 18.2 Hz, 1 H, -C(O)CHH-), 3.00-3.08 (m, 1 H, CH), 4.46-4.49 (m, 1 H, -C(OH)H-), 5.08-5.11 (m, 1 H, -OCHH-).

7-Hydroxy-3-oxabicyclo[3.3.0]octan-2-one (minor isomer): 1H NMR (CDCl$_3$, 500 MHz) δ 1.83-2.28 (m, 5 H), 3.00-3.08 (m, 2 H, CH), 4.24 (dd, J = 2.8, 9.3 Hz, 1 H, -OCHH-), 4.44-4.46 (m, 1 H, -C(OH)H-), 4.53-4.86 (m, 1 H, -OCHH-).

Oxidation of Bicyclo[3.2.0]hept-2-en-6-one.

2-Octabicyclo[3.3.0]octan-6-one (major isomer): 1H NMR (CDCl$_3$, 500 MHz) δ 2.45 (dd, J = 1.7, 18.2 Hz, 1 H), 2.71-2.82 (m, 3 H), 3.50-3.54 (m, 1 H), 5.13-5.15 (m, 1 H, -OCHH-), 5.58-5.60 (m, 1 H, CH=CH), 5.79-5.81 (m, 1 H,
3-Oxabicyclo[3.3.0]oct-6-en-2-one (minor isomer): $^1$H NMR (CDCl$_3$, 500 MHz) δ 2.71-2.82 (m, 3 H), 3.14 (dt, J = 2.2, 7.9 Hz, 1 H), 3.58-3.62 (m, 1 H), 4.25 (dd, J = 1.7, 9.2 Hz, 1 H, -OCH-), 4.44 (dd, J = 7.0, 9.5 Hz, 1 H, -OCH-), 5.65-5.68 (m, 1 H, CH=CH), 5.86-5.89 (m, 1 H, CH=CH).

**Competitive Oxidation of 3-(2-Naphthyl)cyclobutanone (1) and Cyclooctene by Flavin Catalyst/Molecular Oxygen/Zinc System.** A mixture of 1 (49.0 mg, 0.25 mmol), cyclooctene (31.6 mg, 0.25 mmol), DMRFlEt$^+$-ClO$_4^-$ (2.7 mg, 0.005 mmol), diethylene glycol diethyl ether (8.11 mg, internal standard), and zinc dust (19.6 mg, 0.30 mmol) in a mixed solvent of acetonitrile, ethyl acetate, and water (8:1:1, v/v, 0.25 mL) was stirred at 60 °C for 12 h under molecular oxygen. The yields of the lactone and cyclooctene oxide were determined to be 97% and 0%, respectively by means of GC analysis.

**Competitive Aerobic Oxidation of 1 and Methyl $p$-Tolyl Sulfide by Flavin Catalyst/Molecular Oxygen/Zinc System.** A mixture of 1 (39.2 mg, 0.20 mmol), methyl $p$-tolyl sulfide (27.6 mg, 0.20 mmol), DMRFlEt$^+$-ClO$_4^-$ (2.2 mg, 0.004 mmol), diethylene glycol diethyl ether (6.49 mg, internal standard), and zinc dust (19.6 mg, 0.30 mmol) in a mixed solvent of acetonitrile, ethyl acetate, and water (8:1:1, v/v, 0.20 mL) was stirred at 60 °C for 6 h under molecular oxygen. The yields of the lactone, methyl $p$-tolyl sulfoxide, and methyl $p$-tolyl sulfone were determined to be 88%, 3%, and 0%, respectively by means of GC analysis.

**Competitive Oxidation of 1 and Cyclooctene with mCPBA.** A mixture of 1 (49.0 mg, 0.25 mmol), cyclooctene (31.6 mg, 0.25 mmol), NaHCO$_3$ (21.0 mg, 0.25 mmol), and diethylene glycol diethyl ether (8.11 mg, internal standard) in CH$_2$Cl$_2$ (0.75 mL) was placed in a test tube, and 80% mCPBA (64.7 mg, 0.30 mmol) was added in a limited portion. After stirring at 25 °C for 5 h, the yields of the lactone and cyclooctene oxide were determined to be 19% and 94%, respectively by means of GC analysis.

**Competitive Oxidation of 1 and Methyl $p$-Tolyl Sulfide with mCPBA.** A mixture of 1 (39.2 mg, 0.20 mmol), methyl $p$-tolyl sulfide (27.6 mg, 0.20 mmol), NaHCO$_3$ (16.8 mg, 0.20 mmol), and diethylene glycol diethyl ether (6.49 mg, internal standard) in CH$_2$Cl$_2$ (0.5 mL) was placed in
a test tube, and 80% mCPBA (51.8 mg, 0.24 mmol) was added in a limited portion. After stirring at 25 °C for 24 h, the yields of the lactone, methyl \(p\)-tolyl sulfoxide, and methyl \(p\)-tolyl sulfone were determined to be 0%, 53%, and 33%, respectively by means of GC analysis.

**Competitive Oxidation of 1 and Methyl \(p\)-Tolyl Sulfide by Flavin Catalyst/Hydrogen Peroxide System.** A mixture of 1 (39.2 mg, 0.20 mmol), methyl \(p\)-tolyl sulfide (27.6 mg, 0.20 mmol), DMRFlEt\(^{+}\)ClO\(\text{4}^{-}\) (2.2 mg, 0.004 mmol), diethylene glycol diethyl ether (6.49 mg, internal standard), and 30% aqueous H\(_2\)O\(_2\) solution (27.2 mg, 0.24 mmol) in a mixed solvent of acetonitrile and ethyl acetate (8:1, v/v, 0.18 mL) was stirred at 25 °C for 8 h. The yields of the lactone, methyl \(p\)-tolyl sulfoxide, and methyl \(p\)-tolyl sulfone were determined to be 32%, 87%, and 0%, respectively by means of GC analysis.

**Competitive Aerobic Oxidation of 1 and Methyl \(p\)-Tolyl Sulfide by Flavin Catalyst/Molecular Oxygen/Zinc System in CF\(_3\)CH\(_2\)OH-EtOAc-H\(_2\)O.** A mixture of 1 (39.2 mg, 0.20 mmol), methyl \(p\)-tolyl sulfide (27.6 mg, 0.20 mmol), DMRFlEt\(^{+}\)ClO\(\text{4}^{-}\) (2.2 mg, 0.004 mmol), diethylene glycol diethyl ether (6.49 mg, internal standard), and zinc dust (19.6 mg, 0.30 mmol) in a mixed solvent of 2,2,2-trifluoroethanol, ethyl acetate, and water (8:1:1, v/v, 0.20 mL) was stirred at 60 °C for 8 h under molecular oxygen. The yields of the lactone, methyl \(p\)-tolyl sulfoxide, and methyl \(p\)-tolyl sulfone were determined to be 48%, 58%, and 0%, respectively by means of GC analysis.

**References**
