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Ruthenium tetroxide oxidation of cyclic *N*-acylamines by a single layer method: formation of ω-amino acids

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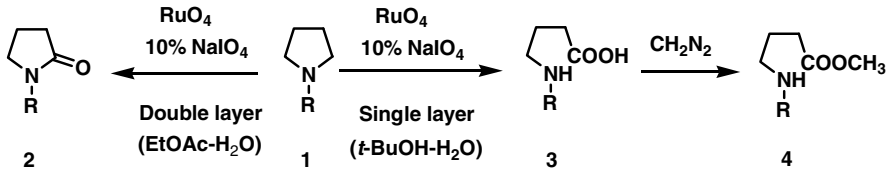
Abstract

The ruthenium tetroxide oxidation of cyclic *N*-acyl amines by a 10% $NaIO_4$ aqueous solution containing *tert*-butanol as a single layer system resulted in the *endo*-cyclic C–N bond cleavage to afford the ω-amino acids as almost sole products in good yields, while a similar oxidation under the double layer using a $NaIO_4$ aqueous solution, and ethyl acetate gave the *N*-acyl lactams.

Keywords: Ruthenium tetroxide oxidation; Single layer system; Double layer system; Cyclic *N*-acylamine; ω-Amino acid

Ruthenium tetroxide (RuO_4) is well known as a highly effective oxidant,[1,2] and very useful for the transformation of cyclic[3] and acyclic[4] *N*-acyl amines into the corresponding lactams and imides. The double layer oxidation method[5] using a catalytic amount of RuO_2 hydrate, an excess of a $NaIO_4$ aqueous solution and ethyl acetate system was established for these purposes in our laboratory. We have previously reported the preparation of various *N*-acyl lactams[3] including the natural products[6] by the double layer RuO_4 oxidation. Recently, the first direct conversion of cyclic *N*-acyl amines to *N*-acyl amino acids via oxidative C–N bond cleavage with pyridine *N*-oxides catalyzed by a ruthenium porphyrin was reported by Higuchi and co-workers.[7] We now wish to describe a similar simple RuO_4 oxidation of various *N*-acyl cyclic amines into the corresponding *N*-acyl amino acids in a $NaIO_4$ aqueous solution containing *tert*-butanol (single layer system).

The oxidation of the five-membered *N*-acyl pyrrolidine **1** was performed with RuO_4 using $NaIO_4$ as a co-oxidant. The RuO_4 oxidation of *N*-benzoylpyrrolidine **1a** under the conventional double layer system (10% $NaIO_4$ solution–ethyl acetate) gave lactam **2a** in almost quantitative yield (Table 1, entry 1). To our surprise, **1a** was oxidized under single layer system using a 10% $NaIO_4$ solution containing *tert*-butanol at room temperature to give 4-aminobutanoic acid **3a** and lactam (2-pyrrolidinone) **2a** in 64% and



Scheme 1.

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Table 1
RuO_4 oxidation of *N*-acyl pyrrolidines **1** via Scheme 1

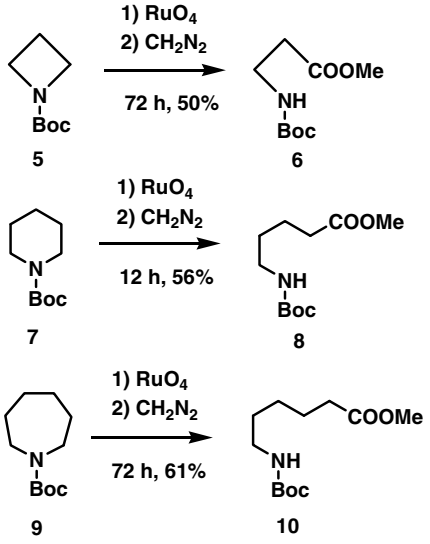
Entry	R	Conditions (additional media)[a]	Time (h)	Products (yield %)[b]
1	Bz[e]	D[c] (AcOEt)	2	**2a** (99)
2	Bz	S[d] (*tert*-BuOH)	5	**2a** (6) **3a** (64)
3[b]	Boc[f]	S (*tert*-BuOH)	4	**4b** (79)
4	Boc	S (Acetone)	6	**4b** (78)
5	Boc	S (Acetonitrile)	6	**4b** (78)
6	Troc[g]	S (*tert*-BuOH)	6	**2c** (3) **4c** (49)
7	Z[h]	S (*tert*-BuOH)	3	**4d** (53)

[a] Reaction condition: substrate, 6 mmol; $RuO_2 \cdot xH_2O$, 60 mg; 10% $NaIO_4$, 80 mL, additional media, 20 mL, room temperature.
[b] Isolated yields.
[c] Double layer.
[d] Single layer.
[e] Benzoyl.
[f] *tert*-Butoxycarbonyl.
[g] 2,2,2-Trichloroethoxycarbonyl.
[h] Benzyloxycarbonyl.

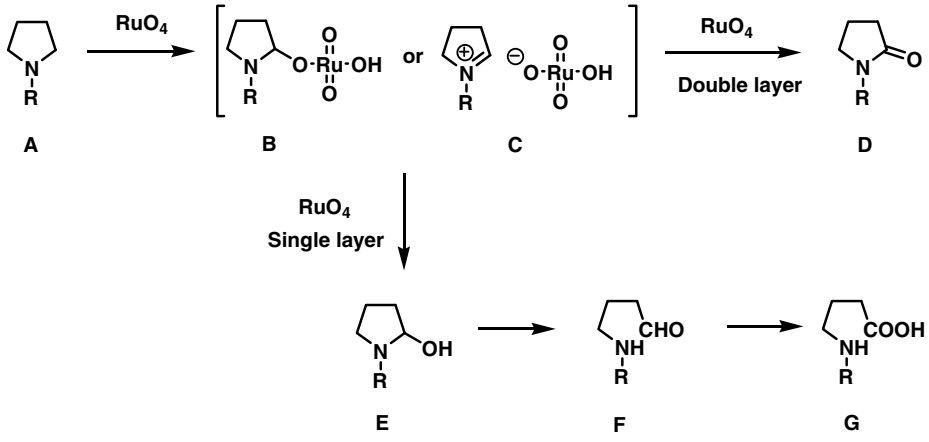
6% yields, respectively (entry 2).[8] The former is the *endo* C–N bond cleavage product, and the latter is formed by the general carbonylation at the C-2 position of the pyrrolidine ring. In contrast, the RuO_4 oxidation of *N*-*tert*-butoxycarbonyl(Boc)pyrrolidine **1b** gave only 4-aminobutanoic acid **3b**, which was isolated as the methyl ester **4b** by treatment of the crude product with diazomethane in ether in 79% yield (entry 3).[9] Using acetone or acetonitrile, which were miscible in water, instead of *tert*-butanol afforded almost similar results (entries 4 and 5). Replacement of the N-protect group from the Boc group to the 2,2,2-trichloroethoxycarbonyl (Troc) or benzyloxycarbonyl group (Z) reduced the yields of the 4-aminobutanoic acids **3c**,**d**, and a small amount of lactams **2c** were produced (entries 6 and 7). In these cases, the 4-aminobutanoic acids **3c**,**d** were also isolated as the corresponding methyl esters **4c**,**d** by the treatment of the crude products with diazomethane (Scheme 1).

A possible mechanism for the formation of the ω-amino acid **G** from the *N*-acylpyrrolidine **A** is shown in Scheme 2. The initial oxidized intermediate, the ruthenate ester **B** or *N*-acyliminium ruthenate **C** generated by the oxidative attack of RuO_4 at the C-2 position of the *N*-acylamine **A**, undergoes hydrolysis to form the 2-hydroxyl amine **E**. The tautomerism with the migration of the hydroxyl proton of **E** produces the ring opening aldehyde **F**, which is further oxidized by RuO_4 to afford the ω-amino acid **G**. In the case of the double layer system (10% $NaIO_4$ solution–ethyl acetate), the ruthenate ester **B** is further oxidized to afford lactam **D**. When the substrate is oxidized under the single layer system, the hydrolysis of the ruthenate ester intermediate **B** or the nucleophilic attack of H_2O on the inium salt **C** is favored due to the aqueous condition. In addition, the isolated 2-hydroxyl amine **E** was easily oxidized to give the ω-amino acid **G** under the single layer system in good yield, although the oxidation of **E** under the double layer system gave lactam **D** in ca. 40% yield.

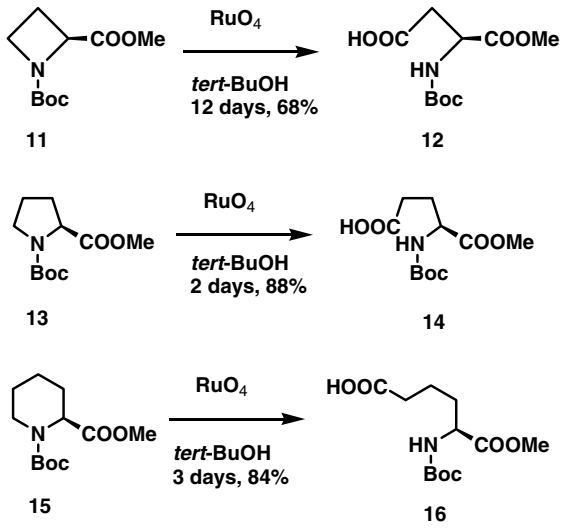
Four-, six-, and seven-membered cyclic *N*-Boc amines **5**, **7**, **9** were also transformed into the corresponding *N*-Boc ω-amino acid methyl esters **6**, **8**, **10** in moderate yields by the RuO_4 oxidation under the similar conditions followed by diazomethane esterification, respectively (Scheme 3).



Scheme 3.



Scheme 2.



Scheme 4.

Next, we planned the deployment of this single layer RuO_4 oxidation into the optically active compounds. Four-membered *N*-Boc cyclic imino acid ester **11** was oxidized under similar conditions to give the corresponding optically active ω-amino acid **12** [$[\alpha]_D^{19}$ −19.9° (lit.[10] $[\alpha]_D^{23}$ −19°)] in 68 yield without any loss of chirality at the C-2 position of the cyclic amine **11**. Similarly, the optically active ω-amino acids **14** and **16** were obtained by the oxidation of the corresponding imino acid esters **13** and **15** in 88% and 84% yields, respectively (Scheme 4).

In summary, simple RuO_4 oxidized cyclic *N*-acylamines to afford ω-amino acids under a single layer system using a $NaIO_4$ solution containing *tert*-butanol in moderate to good yields. This oxidative system can successfully be applied to optically active cyclic imino acid esters producing ω-amino acids having an ester moiety at the α position of the amino group. A significant reaction mechanism of this oxidation reaction is proposed.

Acknowledgments

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8. *Typical procedure for the RuO_4 oxidation of N-acylamino acid to* ω-*amino acid*: A solution of *N*-benzoylpyrrolidine (**1a**, 6 mmol) to be oxidized in *tert*-butanol (20 mL) was added to a mixture of $RuO_2{\cdot}xH_2O$ (60 mg) and 10% $NaIO_4$ aqueous solution (80 mL). The aqueous mixture was vigorously stirred in a sealed flask at room temperature for 5 h. After the starting material had disappeared, ethyl acetate (100 mL) and water (50 mL) were added to the mixture, the organic layer was separated. The aqueous layer was extracted with ethyl acetate (50 mL × 2), and then isopropanol (3 mL) was added to the combined organic mixture. The mixture was stirred for further 2 h for the decomposition of the RuO_4 oxidant, and the black precipitate (RuO_2) was filtered off. The filtrate was washed with brine (50 mL × 2), dried over Na_2SO_4, and then evaporated. The resulting crude acid was purified by column chromatography on silica gel to give **3a** (64%, colorless prisms, mp 77–78 °C) and **2a** (6%, colorless prisms, mp 89–90 °C). Compounds **3a**[11] and **2a**[12] were identical with authentic samples, respectively.
9. *Typical procedure for the preparation of N-acyl* ω-*amino acid methyl ester*: *N-tert*-Butoxycarbonylpyrrolidine (**1b**, 6 mmol) was oxidized and worked up as described for the preparation of **3a** to give the crude acid **3b**. Excess ethereal diazomethane was added to acid **3b** in MeOH (30 mL). The reaction mixture was stirred at room temperature for 1 h, and evaporated. The obtained crude ester was purified by short column chromatography on silica gel to give **4a** (79%) as a colorless oil. IR (KBr): *ν*; 3373 (NH), 1738 (COOMe), 1716 (COO*t*-Bu); MS: *m*/*z*: 216 (M^+-1); HRMS: calcd for $C_{10}H_{18}NO_4$ (M^+-1) 216.1236. Found: 216.1239; ^1H NMR (500 MHz, $CDCl_3$): δ 1.44 (9H, s, *t*-Bu), 1.79–1.82 (2H, m, 3-H), 2.36 (2H, t, $J = 6.4$ Hz, 2-H), 3.16 (2H, q, $J = 6.5$ Hz, 4-H), 3.68 (3H, s, OMe), 4.70–4.82 (1H, br s, NH); ^{13}C NMR (125 MHz, $CDCl_3$): δ 25.3 (t, C3), 28.41 and 79.2 (q and s, *t*-Bu), 31.3 (t, C2), 39.9 (t, C4), 51.7 (q, OMe), 156.0 (s, NC═O), 173.8 (s, C1).
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