Novel Oxidation Reaction of Tertiary Amines with Osmium Tetroxide

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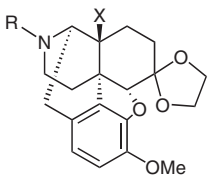
Abstract: Tertiary amines were oxidized with OsO_4 to afford mixtures of lactams, hydroxylactams, and ketolactams. In contrast to RuO_4, which was known to oxidize tertiary amines, amides, and *N*-carbamoylamines, OsO_4 oxidized the tertiary amines exclusively and tolerated amides and *N*-carbamoylamines. A mechanism for the oxidation reaction is also proposed.

Key words: osmium tetroxide, oxidation, tertiary amine, 4,5-epoxymorphinan, opioid

Osmium tetroxide is one of the most reliable reagents for dihydroxylation of olefins,[1,2] and conditions for asymmetric dihydroxylation of olefins using OsO_4 with a chiral amine ligand have also been developed.[2] Therefore, OsO_4 is widely used in organic synthesis despite being an expensive and toxic reagent. Other than the dihydroxylation of olefins, OsO_4 has also been used for oxidation of alcohols to aldehydes or ketones,[3] of sulfides or sulfoxides to sulfones,[4] of acetylenes to α-diketones,[1a,5] and of benzylic primary amines to nitriles,[6] as well as for the dihydroxylation of C–C double bonds in homo- and hetero-aromatic rings.[7] To the best of our knowledge, the oxidation of tertiary amines with OsO_4 has not yet been reported, although some amines have been used as chiral ligands for asymmetric dihydroxylation.[2] In the course of our investigations of opioid compounds, we found that 4,5-epoxymorphinan derivatives were oxidized with OsO_4 to give some oxidation products: hydroxylactams, ketolactams, amides, and so on. Here, we report novel oxidation reactions of tertiary amines (4,5-epoxymorphinan derivatives and 4-aryl piperidine derivatives) by OsO_4, and we propose a plausible mechanism.

4,5-Epoxymorphinan derivatives **1a**–**c**[8,9] were oxidized with OsO_4 to afford amides **2a**–**c**, ketolactams **3** and **4a**–**c**, and hydroxylactams **5a**–**c** (Table 1). In the case of the oxidation reaction of compound **1a**, lactam **6a**, and iminoketone **7** were also obtained (Table 1, entries 1, 2). Under the stoichiometric reaction conditions [conditions I: OsO_4 (3 equiv), pyridine, r.t.], the main product was amide **2** (Table 1, entries 1, 3, and 5), while ketolactams **3** and **4**, and hydroxylactam **5** were mainly obtained under the catalytic reaction conditions [conditions II: OsO_4 (0.1 equiv), $K_3Fe(CN)_6$ (9 equiv), K_2CO_3 (9 equiv), *t*-BuOH–H_2O = 1:1, r.t.][10] (Table 1, entries 2, 4, and 6). The oxidation rate seemed to be faster in conditions I than in conditions II except for the case of *N*-cyclopropylmethyl (CPM) derivative **1a**. The reaction of hydroxy derivative **1d**[8b,11] (Figure 1) was slower even at 50 °C, and a large amount of the starting material **1d** was recovered.



1a–h

a R = CPM, X = H
b R = Me, X = H
c R = *i*-Bu, X = H
d R = CPM, X = OH
e R = Troc, X = H
f R = Boc, X = H
g R = Ac, X = H
h R, X = H

Figure 1 Structures of compound **1**

We propose one possible mechanism that the oxidation reaction of compound **1** proceeds via the sequence of mechanisms depicted in Scheme 1. The oxidation reaction would commence with the coordination of nitrogen to osmium followed by elimination. Enamine **10**, which was prepared by imine–enamine equilibrium, would be oxidized with OsO_4 to give osmate ester **11**.[12,13] When both protons located at the oxygens of the osmate ester were deprotonated,[14] ketolactam **4** would be obtained. On the other hand, if the single, more acidic proton located at the α-position with respect to the nitrogen was deprotonated, but another less acidic proton was not deprotonated, and if the Os–O bond of the osmate ester was hydrolyzed, hydroxylactam **5** may be obtained. Another plausible mechanism cannot be denied: aminal moiety in diol obtained from **11** would be oxidized to give hydroxylactam **5**, which would be further oxidized to afford ketolactam **4**. If the elimination of osmic acid took place at the side of the nitrogen substituent in **8′** to give iminium **9′**, amide **2** would be produced.[15]

The oxidation rate of **1d** was much slower than that of **1a**. Disturbance of the initial coordination of the basic nitrogen in **1d** with osmium by formation of a strong intramolecular hydrogen bond between the basic nitrogen and the hydroxy proton[16] could account for this outcome.

Exposure of amides **2a**–**c** to OsO_4 (conditions II) resulted in the recovery of starting material **2** (Scheme 2). These results seemed at odds with the following paths of preparation of compound **3**: Hydrolysis of compound **2** and subsequent oxidation reaction would give compound **3**; compound **2** would then be further oxidized to afford the

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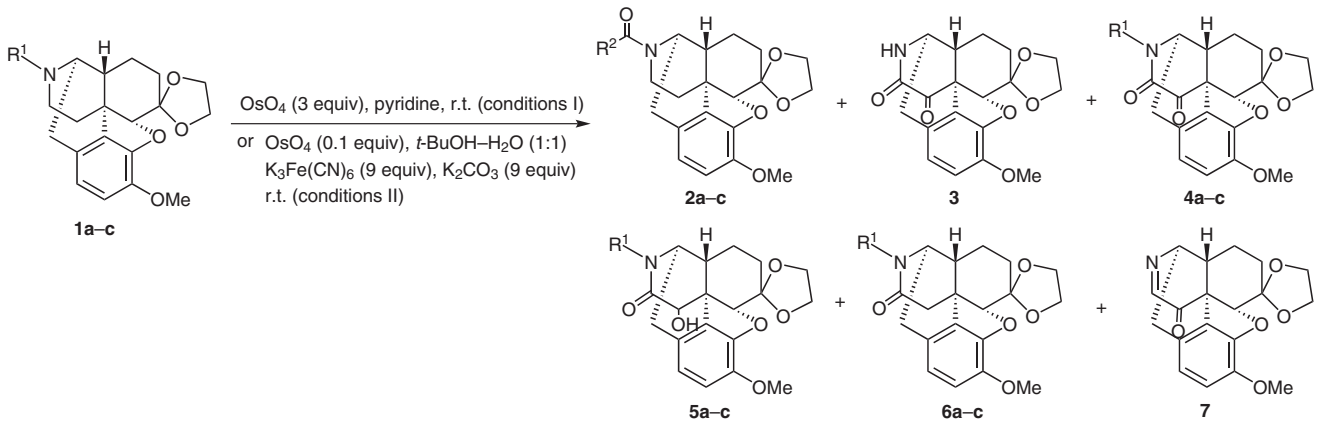
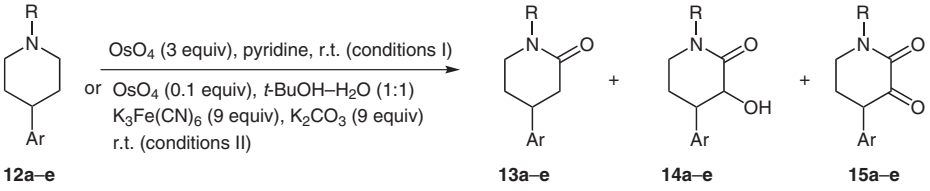
Table 1 Oxidation Reaction of 4,5-Epoxymorphinan Derivative **1** with OsO_4[21,22]



Entry	Starting material	R^1	R^2	Conditions	Isolated yield (%)						Time (h)
					2	**3**	**4**	**5**[a]	**6**	**7**	
1	**1a**	CPM[b]	CP[c]	I	40	9	7	11	5	–[d]	72
2	**1a**	CPM[b]	CP[c]	II	–[d]	44	4	40	2	7	19
3	**1b**	Me	H	I	39	9	16	–[d]	–[d]	–[d]	24
4	**1b**	Me	H	II	18	14	24	3	–[d]	–[d]	188
5	**1c**	*i*-Bu	*i*-Pr	I	40	–[d]	26	19	–[d]	–[d]	12
6	**1c**	*i*-Bu	*i*-Pr	II	–[d]	26	9	24	–[d]	–[d]	144

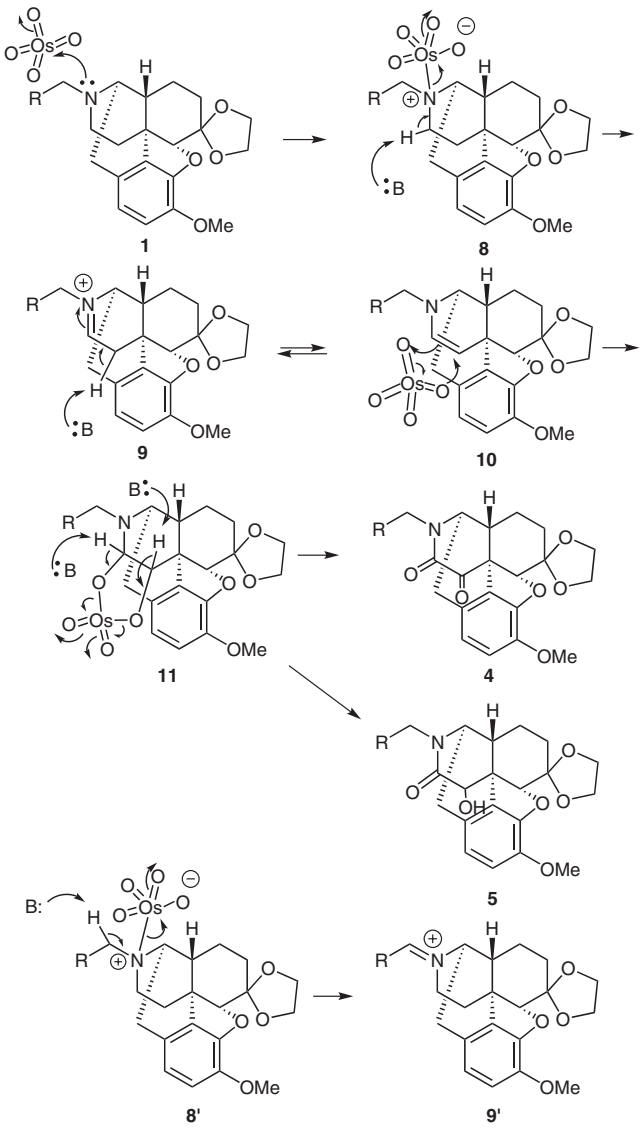
[a] The stereochemistry of the hydroxy group was not determined.
[b] Cyclopropylmethyl.
[c] Cyclopropyl.
[d] Not determined.

Table 2 Oxidation Reaction of 4-Arylpiperidine Derivative **12** with OsO_4[21]



Entry	Starting material	R	Ar	Conditions	Isolated yield (%)			Time (h)
					13	**14**	**15**	
1	**12a**	CPM[a]	2-naphthyl	I	43	–[b]	–[b]	136
2	**12a**	CPM[a]	2-naphthyl	II	–[b]	16	–[b]	168
3	**12b**	Me	2-naphthyl	I	49	–[b]	–[b]	180
4	**12b**	Me	2-naphthyl	II	20	17	–[b]	164
5	**12c**	*i*-Bu	2-naphthyl	I	39	–[b]	–[b]	6
6	**12c**	*i*-Bu	2-naphthyl	II	10	18	16	168
7	**12d**	Me	Ph	I	43	–[b]	–[b]	24
8	**12d**	Me	Ph	II	13	9	–[b]	432
9	**12e**	H	2-naphthyl	II	–[b]	–[b]	–[b]	160

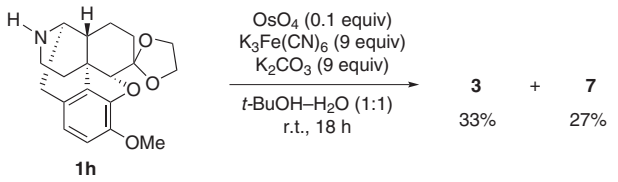
[a] Cyclopropylmethyl.
[b] Not determined.



Scheme 1 Plausible mechanism of the oxidation reaction

imide, which would be converted into compound **3** by hydrolysis. Moreover, the results supported the proposed reaction mechanism beginning with the coordination of basic nitrogen to osmium.

Our attempts to perform the oxidation reaction on the secondary amine **1h** with OsO_4 gave compounds **3** and **7** in 33% and 27% yield, respectively (Scheme 3). This result suggests that compound **3** may be prepared from NH derivative **1h** obtained by hydrolysis of iminium intermediate **9′**.

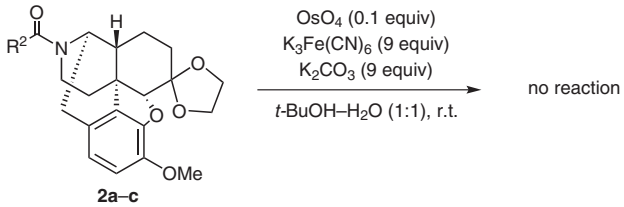


Scheme 3 Oxidation reaction of the secondary amine **1h** with OsO_4

We next applied the oxidation reaction to general amines. The oxidation reaction of 4-arylpiperidine **12** with OsO_4 gave lactam **13**, hydroxylactam **14**, and/or ketolactam **15** (Table 2). These results suggest that the oxidation reaction with OsO_4 can be generally applied to tertiary amines. However, the oxidation reaction of the secondary amine **12e** gave a complex mixture (Table 2, entry 9). This result was in sharp contrast to that of compound **1h**. We believe that this discrepancy would result from the differences in the steric hindrance between compounds **1h** and **12e**. Less hindered **12e** could add to the intermediate iminium and give a diamine species, which could then be converted to another iminium, which may afford a complex mixture.

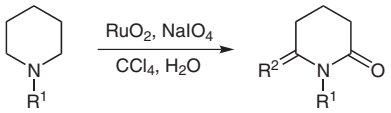
On the other hand, compound **1h** was so hindered that it could hardly add to the intermediate iminium to afford the oxidation products **3** and **7**. In the oxidation of 4-arylpiperadine derivative **12**, acyclic amide in which oxidation took place at the side of the nitrogen substituent R was not detected, although the oxidation of 4,5-epoxymorphinan derivative **1** gave both amide **2** and lactam like **3**–**6**. 4-Arylpiperadine derivative **12** may be converted to lactams **13**–**15** via more stable cyclic iminium predominantly. On the other hand, the steric hindrance by methylene bridge and/or benzene ring in 4,5-epoxymorphinan derivative **1** may make formation of cyclic iminium **9** slower to afford both cyclic and acyclic iminium (**9** and **9′**).

Ruthenium and osmium are congeners, so ruthenium tetroxide is also a powerful oxidizing agent and is widely used in organic synthesis.[17,18] As opposed to OsO_4, RuO_4 has been reported to oxidize tertiary amines, amides, or *N*-carbamoylamines to give imides or *N*-carbamoylamides, respectively (Scheme 4).[19] To compare the reactivity between OsO_4 and RuO_4, oxidation reactions of compounds **1e**–**g**[20] (Figure 1) with OsO_4 or RuO_4 were attempted. In the oxidation reactions of compounds **1e**–**g** with OsO_4 under both stoichiometric and catalytic conditions, no products were obtained and only starting material was recovered. In contrast, oxidation reaction of compound **1e** with RuO_4, which was prepared from RuO_2 and $NaIO_4$ in situ, gave an intractable mixture. These results indicated



Scheme 2 Exposure of amides **2a**–**c** to OsO_4

that OsO_4 could selectively oxidize only the tertiary amines.



16a–c **17a–c**

a R^1 = Bn, R^2 = O
b R^1 = Ac, R^2 = H, H
c R^1 = EtOCO, R^2 = H, H

Scheme 4 Oxidation reaction of compounds **16a–c** with RuO_4[19]

In conclusion, we found that tertiary amines (4,5-epoxymorphinan derivatives and 4-arylpiperidine derivatives) were oxidized with OsO_4 to give amides (lactams), hydroxylactams, and/or ketolactams. The oxidation reaction was chemoselective and tolerated amides and *N*-carbamoylamines. A mechanism of the oxidation reaction was also proposed.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(14) In the Supporting Information, the deprotonation of osmate ester is discussed in detail.

(15) Plausible mechanisms to amide **2** and lactam **6** are described in the Supporting Information.

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(21) **Oxidation of Amine with OsO_4**

Stoichiometric Reaction Conditions: Conditions I

To the solution of amine in pyridine was added OsO_4 (3 mol equiv) and stirred at r.t. for the time indicated in Tables 1 and 2. The aqueous solution of Na_2SO_3 was added to the reaction mixture and stirred vigorously at r.t. for several hours. The resulting mixture was evaporated under reduced pressure and extracted with $CHCl_3$. The organic layer was washed with brine and dried over Na_2SO_4. After removing the solvent under reduced pressure, the residue was purified by silica gel column chromatography and/or preparative TLC.

Catalytic Reaction Conditions: Conditions II

Amine was added to the solution of $K_3Fe(CN)_6$ (9 mol equiv), K_2CO_3 (9 mol equiv), and OsO_4 (0.1 mol equiv) in *t*-BuOH and distilled H_2O (1:1) and stirred at r.t. for the time indicated in Tables 1 and 2. To the reaction mixture was added the aqueous solution of Na_2SO_3 and stirred at r.t. for several hours. The resulting mixture was poured into distillated H_2O and extracted with $CHCl_3$. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography and/or preparative TLC.

(22) **Amide 2a**

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.67–1.25 (m, 5 H), 1.44–1.86 (m, 6 H), 1.93–2.02 (m, 0.7 H), 2.07–2.15 (m, 0.3 H), 2.54–2.63 (m, 0.3 H), 2.62 (d, *J* = 18.3 Hz, 0.7 H), 2.76 (d, *J* = 18.0 Hz, 0.3 H), 2.90 (dd, *J* = 5.9, 18.3 Hz, 0.7 H), 3.00 (dd, *J* = 5.4, 18.0 Hz, 0.3 H), 3.05–3.18 (m, 0.7 H), 3.76–3.93 (m, 2 H), 3.89 (s, 3 H), 3.96–4.09 (m, 1.7 H), 4.14–4.24 (m, 1 H), 4.38–4.47 (m, 0.3 H), 4.49 (s, 1 H), 4.65 (br s, 0.3 H), 5.10–5.16 (m, 0.7 H), 6.64 (br d, *J* = 8.4 Hz, 1 H), 6.78 (d, *J* = 8.1 Hz, 1 H). IR (film): 3467, 2947, 1632, 1502, 1437, 1261, 1168, 1017 cm^{-1}. HRMS–FAB: *m/z* calcd for $C_{23}H_{28}NO_5$ [M + H]$^+$: 398.1962; found: 398.1976.

Ketolactam 3

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.31–1.58 (m, 2 H), 1.66–1.82 (m, 2 H), 2.63–2.73 (m, 1 H), 2.78–2.96 (m, 2 H), 3.71–4.03 (m, 4 H), 3.87 (s, 3 H), 4.20–4.29 (m, 1 H), 5.42 (s, 1 H), 6.67 (d, *J* = 8.1 Hz, 1 H), 6.86 (d, *J* = 8.4 Hz, 1 H), 7.74 (br s, 1 H). IR (film): 1736, 1694 cm^{-1}. HRMS–FAB: *m/z* calcd for $C_{19}H_{20}NO_6$ [M + H]$^+$: 358.1291; found: 358.1300.

Ketolactam 4a

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.28–0.40 (m, 2 H), 0.49–0.69 (m, 2 H), 1.03–1.18 (m, 1 H), 1.35–1.61 (m, 2 H), 1.66–1.86 (m, 2 H), 2.67–2.76 (m, 1 H), 2.78 (dd, *J* = 4.2, 17.7 Hz, 1 H), 2.93 (dd, *J* = 6.9, 14.1 Hz, 1 H), 3.04 (dd, *J* = 1.2, 17.7 Hz, 1 H), 3.75–4.10 (m, 5 H), 3.86 (s, 3 H), 4.21–4.29 (m, 1 H), 5.40 (s, 1 H), 6.65 (d, *J* = 8.1 Hz, 1 H), 6.84 (d, *J* = 8.1 Hz, 1 H). IR (film): 2923, 1733, 1670 cm^{-1}. HRMS–FAB: *m/z* calcd for $C_{23}H_{26}NO_6$ [M + H]$^+$: 412.1760; found: 412.1776.

Hydroxylactam 5a

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.21–0.36 (m, 2 H), 0.45–0.65 (m, 2 H), 0.99–1.13 (m, 1 H), 1.17–1.35 (m, 1 H), 1.51–1.77 (m, 3 H), 2.60–2.71 (m, 2 H), 2.76 (dd, *J* = 7.1, 14.0 Hz, 1 H), 2.89 (br d, *J* = 17.4 Hz, 1 H), 3.71–4.00 (m, 6 H), 3.87 (s, 3 H), 4.17–4.25 (m, 1 H), 5.17 (s, 1 H), 6.59 (d, *J* = 8.1 Hz, 1 H), 6.79 (d, *J* = 8.1 Hz, 1 H). One proton of the OH group was not observed. IR (film): 3294, 2928, 1623, 1503, 1439, 1276, 1194, 1055 cm^{-1}. HRMS–FAB: *m/z* calcd for $C_{23}H_{28}NO_6$ [M + H]$^+$: 414.1917; found: 414.1896.

Lactam 6a

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.21–0.34 (m, 2 H), 0.45–0.63 (m, 2 H), 0.98–1.12 (m, 1 H), 1.18–1.35 (m, 1 H), 1.52–1.77 (m, 3 H), 2.35 (dt, *J* = 12.7, 3.7 Hz, 1 H), 2.61 (d, *J* = 17.1 Hz, 1 H), 2.60–2.77 (m, 2 H), 2.72 (d, *J* = 17.4 Hz, 1 H), 2.93 (dd, *J* = 1.2, 17.4 Hz, 1 H), 3.73–3.81 (m, 1 H), 3.84–4.02 (m, 4 H), 3.87 (s, 3 H), 4.20 (dt, *J* = 5.2, 6.8 Hz, 1 H), 4.49 (s, 1 H), 6.60 (d, *J* = 8.4 Hz, 1 H), 6.77 (d, *J* = 8.1 Hz, 1 H). IR (film): 2923, 1635, 1504, 1440 cm^{-1}. HRMS–FAB: *m/z* calcd for $C_{23}H_{28}NO_5$ [M + H]$^+$: 398.1967; found: 398.1962.

Iminoketone 7

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.28–1.41 (m, 1 H), 1.44–1.54 (m, 1 H), 1.68–1.78 (m, 2 H), 2.45 (ddd, *J* = 3.2, 4.3, 12.3 Hz, 1 H), 2.91 (ddd, *J* = 0.8, 5.4, 17.9 Hz, 1 H), 2.96 (ddd, *J* = 0.7, 2.0, 17.8 Hz, 1 H), 3.77–3.82 (m, 1 H), 3.86 (s, 3 H), 3.91 (dt, *J* = 7.3, 6.5 Hz, 1 H), 4.00 (q, *J* = 6.6 Hz, 1 H), 4.24 (ddd, *J* = 5.4, 6.8, 7.1 Hz, 1 H), 4.54 (ddd, *J* = 1.8, 3.3, 6.7 Hz, 1 H), 5.32 (s, 1 H), 6.66 (d, *J* = 8.2 Hz, 1 H), 6.84 (d, *J* = 8.2 Hz, 1 H), 7.70 (d, *J* = 1.5 Hz, 1 H). IR (film): 2928, 1710, 1606, 1503, 1440, 1279, 1187, 1061 cm^{-1}. HRMS–FAB: *m/z* calcd for $C_{19}H_{20}NO_5$ [M + H]$^+$: 342.1341; found: 342.1335.