Ruthenium Tetroxide Oxidation of 3,4-Dihydroisoquinolin-1(2*H*)-ones: An Efficient Synthesis of Isoquinoline-1,3,4(2*H*)-triones

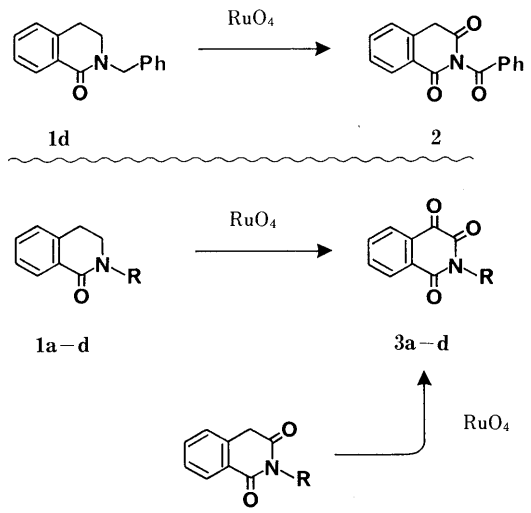
Shigeyuki YOSHIFUJI* and Yukimi ARAKAWA

School of Pharmacy, Hokuriku University, Kanagawa-machi, Kanazawa 920–11, Japan. *Received April 7, 1989*

Ruthenium tetroxide (RuO_4) oxidation of 3,4-dihydroisoquinolin-1(2*H*)-ones produced the corresponding isoquinoline-1,3,4(2*H*)-triones in good yields. In the cases of *N*-alkyl derivatives having two oxidation sites adjacent to the nitrogen atom, regioselective endocyclic oxidation was observed.

Keywords oxidation; ruthenium tetroxide oxidation; imide synthesis; 3,4-dihydroisoquinolin-1(2*H*)-one; isoquinoline-1,3,4(2*H*)-trione; ruthenium tetroxide; regioselectivity

We have presented many examples[1] of the useful transformation of nitrogen-containing compounds by ruthenium tetroxide (RuO_4) oxidation. In previous studies[1f] on *N*-alkyllactams having two oxidation sites adjacent to the nitrogen atom, only one of which is subject to RuO_4 oxidation, high regioselectivity depending on the size of the lactam ring was observed. Six-membered *N*-alkyllactams were oxidized predominantly at the endocyclic α-carbons to produce the corresponding hydroxylactams or cyclic imides and the exocyclic α-carbons were not affected by RuO_4 at all. As an extension of our investigation on the regioselective oxidation, we were interested in the oxidation of *N*-alkyl-3,4-dihydroisoquinolin-1(2*H*)-ones consisting of a six-membered lactam and a fused benzene ring, which should be oxidized at the endocyclic 3-position to afford the corresponding 1,3-dioxo compounds (homophthalimides). Tortorella and co-workers[2] have already reported that the RuO_4 oxidation of *N*-benzyl-3,4-dihydroisoquinolin-1(2*H*)-one (**1d**) gave *N*-benzoyl-homophthalimide (**2**). Formation of the product **2**, whose structure had been proposed without detailed elucidation, was inconsistent with the above-mentioned regioselectivity in the oxidation of six-membered *N*-alkyllactams. We now wish to report new results concerning the RuO_4 oxidation of 3,4-dihydroisoquinolin-1(2*H*)-ones (**1a**—**d**) to form the corresponding isoquinoline-1,3,4(2*H*)-triones (**3a**—**d**), as illustrated in Chart 1.



a: R=H; **b**: R=CH_3; **c**: R=C_2H_5; **d**: R=CH_2Ph

Chart 1

The 3,4-dihydroisoquinolin-1(2*H*)-ones (**1b**—**d**) *N*-substituted with a methyl, ethyl or benzyl group were readily prepared through the alkaline ferricyanide oxidation of the corresponding *N*-alkylisoquinolinium salts and catalytic hydrogenation of the resulting isoquinolones with Raney nickel.

The RuO_4 oxidation of the *N*-alkyl compounds (**1b**—**d**) was carried out at room temperature according to our improved procedure[1b] using catalytic amounts of ruthenium dioxide ($RuO_2 \cdot xH_2O$) and an excess of 10% aqueous sodium periodate ($NaIO_4$) in a two-phase system of ethyl acetate (AcOEt)–H_2O. The reaction proceeded smoothly with a consistent yellow color which indicated the existence of active RuO_4 generated *in situ* under the above conditions. Products obtained from the organic phase as yellow solids in high yields were assigned as the corresponding isoquinoline-1,3,4(2*H*)-triones (**3b**—**d**) which had three carbonyl carbons on the piperidine ring of the isoquinolines on the basis of analysis of the proton and carbon-13 nuclear magnetic resonance (^1H- and ^{13}C-NMR) spectra. The *N*-benzyl derivative (**1d**), as well as the other substrates (**1b**, **c**), did not provide any products resulting from exocyclic oxidation, such as the *N*-benzoylhomophthalimide (**2**) reported by Tortorella *et al.*[2] The *N*-benzyl structure in **3d** was confirmed by the acid hydrolysis of **3d**, which gave benzylamine.[3]

By the same procedure, the *N*-unsubstituted isoquinolone (**1a**) was oxidized with RuO_4 to yield the 1,3,4-trione (**3a**) in 88% yield, but a long reaction time was required. On the other hand, homophthalimide (**4a**) was rapidly oxidized to **3a** in 96% yield under the same conditions. Since thin layer chromatographic (TLC) analysis during the oxidation of **1a** suggested that the homophthalimide (**4a**) was present in the initial stage of the reaction, **4a** might be an intermediate of the oxidation of **1a** to **3a**. Similarly, *N*-benzylhomophthalimide (**4d**) was oxidized with RuO_4 to **3d** in 88% yield. Results for all the oxidations are summarized in Table I.

Thus, it was found that the RuO_4 oxidation of *N*-alkyl-3,4-dihydroisoquinolin-1(2*H*)-ones proceeded according to the same regioselectivity as seen in the oxidation of *N*-alkyllactams to yield initially the endocyclic oxidation products, *N*-alkylhomophthalimides, and then further oxidation occurred at the C-4 position of the homophthalimides to furnish *N*-alkylisoquinoline-1,3,4(2*H*)-triones.

TABLE I. RuO_4 Oxidation of **1a—d** and **4a,d** to Isoquinoline-1,3,4(2*H*)-triones (**3a—d**)

Substrate	Reaction time (h)	Yield (%)	Product	mp (°C)	Reported mp (°C)[8]	^{13}C-NMR (C=O)		$\delta(CDCl_3)$
1a	8	88	**3a**	229—229.5	221—223	157.6	163.4	175.7[a]
1b	1	94	**3b**	190—191	185—186	157.6	162.6	174.8
1c	1	91	**3c**	107—107.5	102.5—103.5	157.1	162.2	175.0
1d	4	81	**3d**	185—186	181.5—183.5	157.2	162.4	174.8
4a	0.5	96	**3a**					
4d	3.5	88	**3d**					

a) Measured in DMSO-d_6.

This convenient and regioselective oxidation may provide an efficient and general synthetic method for isoquinoline-1,3,4(2*H*)-triones.

Experimental

Melting points were taken on a Yanagimoto melting point apparatus. All melting points are uncorrected. Infrared (IR) spectra were recorded in KBr tablet on a JASCO IRA-2 or a Hitachi 270-30 spectrometer. Mass spectra (MS) were measured on a JEOL JMS D-300 spectrometer. ^{1}H-NMR Spectra were obtained at 23 °C using tetramethylsilane as an internal standard on a JEOL JNM-MH-100 spectrometer. ^{13}C-NMR spectra were measured on a JEOL JNM-FX-100 spectrometer. The following abbreviations are used: m = multiplet, q = quartet, s = singlet, t = triplet.

3,4-Dihydroisoquinolin-1(2*H*)-one (1a) This compound was prepared by the reported method.[4]

***N*-Alkyl-3,4-dihydroisoquinolin-1(2*H*)-ones (1b—d)** These substrates were synthesized according to a procedure patterned after that used by Schneider and Müller.[5] Isoquinoline was quaternized with alkyl halides (methyl iodide, ethyl iodide and benzyl bromide) in boiling benzene. Alkaline ferricyanide oxidation [KOH–$K_3Fe(CN)_6$] of the resulting quaternary salts was carried out at room temperature in a two-phase system of benzene–H_2O to afford *N*-alkylisoquinolin-1(2*H*)-ones. *N*-Alkyl-3,4-dihydroisoquinolin-1(2*H*)-ones (**1b—d**) were obtained from these products by catalytic hydrogenation [Raney nickel (W-2), ethanol, 3.4 atm of H_2, room temperature]. Identification of the products was done by comparison of their physical and spectral data with reported data.

1b[5b,6]: Total yield from isoquinoline was 41%, yellow oil.

1c[6]: Total yield 34%, pale yellow oil.

1d[7]: Total yield 33%, yellow oil.

Standard Procedure for RuO_4 Oxidation of 3,4-Dihydroisoquinolin-1(2*H*)-ones (1a—d) A solution of a substrate (12 mmol) in AcOEt (40 ml) was added to a mixture of $RuO_2 \cdot xH_2O$ [Aldrich Chemical Co.] (120 mg) and 10% aqueous $NaIO_4$ (120 ml). The mixture was vigorously stirred at room temperature. After the starting material had disappeared as determined by TLC, the layers were separated. The aqueous layer was extracted with AcOEt (3 × 20 ml). The combined organic solution was treated with isopropyl alcohol (2 ml) for 3 h to decompose RuO_4 and then the black precipitates (RuO_2) were filtered off. The filtrate was washed with H_2O, and dried over anhydrous Na_2SO_4. The solvent was evaporated *in vacuo* to leave a yellow solid, which was purified by recrystallization.

The results (reaction time, yield, melting point and ^{13}C-NMR data) are summarized in Table I. The identification of the products was based on the following values.

3a[8]: Yellow prisms (from AcOEt). MS *m/z*: 175 (M^+). IR ν_{max} cm^{-1}: 1679, 1705, 1742 (C=O). ^{1}H-NMR (DMSO-d_6) δ: 7.82—8.18 (4H, m, aromatic protons), 11.98 (1H, s, NH). *Anal.* Calcd for $C_9H_5NO_3$: C, 61.72; H, 2.88; N, 8.00. Found: C, 61.76; H, 2.85; N, 7.99.

3b[8,9]: Yellow prisms (EtOH). MS *m/z*: 189 (M^+). IR ν_{max} cm^{-1}: 1667, 1703, 1727 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 3.48 (3H, s, CH_3), 7.76—8.08 (2H, m, C_6-H and C_7-H), 8.16—8.46 (2H, m, C_5-H and C_8-H). *Anal.* Calcd for $C_{10}H_7NO_3$: C, 63.49; H, 3.73; N, 7.40. Found: C, 63.48; H, 3.66; N, 7.42.

3c[8,10]: Yellow prisms (EtOH). MS *m/z*: 203 (M^+). IR ν_{max} cm^{-1}: 1670, 1722 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.24 (3H, t, J = 6.5 Hz, CH_3), 4.16 (2H, q, J = 6.5 Hz, CH_2), 7.76—8.06 (2H, m, C_6-H and C_7-H), 8.20—8.48 (2H, m, C_5-H and C_8-H). *Anal.* Calcd for $C_{11}H_9NO_3$: C, 65.02; H, 4.46; N, 6.89. Found: C, 64.94; H, 4.45; N, 6.87.

3d[8]: Yellow prisms (EtOH). MS *m/z*: 265 (M^+). IR ν_{max} cm^{-1}: 1669, 1704, 1720 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 5.25 (2H, s, CH_2), 7.26—7.64 (5H, m, C_6H_5), 7.80—8.06 (2H, m, C_6-H and C_7-H), 8.20—8.52 (2H, m, C_5-H and C_8-H). *Anal.* Calcd for $C_{16}H_{11}NO_3$: C, 72.45; H, 4.18; N, 5.28. Found: C, 72.43; H, 4.11; N, 5.29.

Hydrolysis of 3d Compound **3d** was hydrolyzed in a 1:1 mixture of 10% aqueous HCl and acetic acid (reflux, 30 h). On work-up after the reaction, benzylamine (77%) was obtained.

RuO_4 Oxidation of Homophthalimides (4a, d) The oxidation of homophthalimides (**4a**[11] and **4d**[12]) was carried out according to the standard procedure as described above, and the corresponding isoquinoline-1,3,4(2*H*)-triones (**3a, d**) were obtained. The results are included in Table I.

References and Notes

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