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Palladium-Catalyzed Hydrogenolysis of Azabicyclic Peroxides. Quantitative Transformation to 1-Hydroxy-7-aza-2-oxabicyclo[3.3.0]octanes

Firoz Alam Chowdhury,[a] Shougo Kajikawa,[a] Hiroshi Nishino,[b]* and Kazu Kurosawa[c]

[a]Department of Environmental Science, Graduate School of Science and Technology, Kumamoto University,
Kurokami 2-39-1, Kumamoto 860-8555, Japan
[b]Department of Chemistry, Faculty of Science, Kumamoto University, Kurokami 2-39-1, Kumamoto 860-8555, Japan
[c]Department of Environmental Science, Faculty of Science, Kumamoto University, Kurokami 2-39-1, Kumamoto 860-8555, Japan

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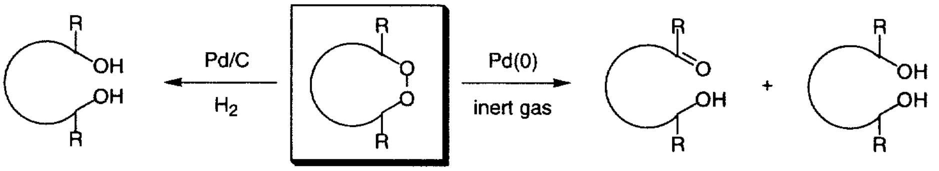
Abstract: The palladium-catalyzed reduction of 1-hydroxy-8-aza-2,3-dioxabicyclo[4.3.0]nonanes, which were readily obtained by the manganese(III)-mediated oxidative formal [2+2+2] cycloaddition of pyrrolidinedione derivatives with alkenes and molecular oxygen, led to formal extrusion of one of the peroxide oxygens and produced 1-hydroxy-7-aza-2-oxabicyclo[3.3.0]octanes in quantitative chemical yields.

Keywords: Palladium-catalyzed hydrogenolysis; Azabicyclic peroxides; Pyrrolidinedione derivatives

Reactions of cyclic peroxides have been well-documented during the last two decades in view of their synthetic and biosynthetic demands.[1] Recently, we have developed a unique and efficient cyclic peroxide synthesis using molecular oxygen and manganese(III) complexes.[2-4] Structure determination of the cyclic peroxides was sometimes difficult because of their structural instability. The most general transformation to characterize the cyclic peroxides is the reductive cleavage of the peroxide linkage. In general, the palladium-catalyzed reaction of cyclic peroxides leads to the corresponding diols and/or hydroxyl ketones.[1c,5] In connection with our recent project on the chemical transformation of cyclic peroxides,[6] we found a quantitative conversion from 1-hydroxy-8-aza-2,3-dioxabicyclo[4.3.0]nonanes to 1-hydroxy-7-aza-2-oxabicyclo-[3.3.0]octanes using palladium-catalyzed hydrogenolysis. Herein we briefly report these results.



Azabicyclic peroxides **3** prepared by the Mn(III)-based oxidation of alkenes **1** with 2,4-pyrrolidinediones **2** according to the literature[2] are stable in dichloromethane or methanol solution. For our initial approach, a mixture of azabicyclic peroxide **3** (R^1, R^2 = Ph, R^3 = CO_2Et, R^4 = Bn) (1 mmol), 10% palladium-carbon (0.1 mmol), and dichloromethane (15 mL) was placed in a stainless steel reaction vessel and sealed. Hydrogen (50 atm) was charged into the reaction vessel followed by heating for one hour. After removal of the palladium-

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*Corresponding author. Hiroshi Nishino, Fax: +81(96)342-3320; E-mail: nishino@aster.sci.kumamoto-u.ac.jp

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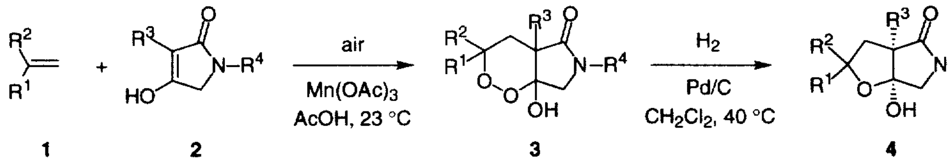

Table 1. Palladium-Catalyzed Reduction of Azabicyclic Peroxides **3** under a Hydrogen Atmosphere[a]

Entry	Azabicyclic peroxide **3**				Reaction time	Reduction product **4**
	R^1	R^2	R^3	R^4	h	yield/%[b]
1	Ph	Ph	CO_2Et	Bn	1	98
2	$4\text{-}MeC_6H_4$	$4\text{-}MeC_6H_4$	CO_2Et	Bn	1	100
3	$4\text{-}MeOC_6H_4$	$4\text{-}MeOC_6H_4$	CO_2Et	Bn	1	98
4[c]	$4\text{-}ClC_6H_4$	$4\text{-}ClC_6H_4$	CO_2Et	Bn	1.3	98
5	$4\text{-}FC_6H_4$	$4\text{-}FC_6H_4$	CO_2Et	Bn	1.3	99
6	Me	Ph	CO_2Et	Bn	1	100
7	Me	Me	CO_2Et	Bn	1	95
8	Ph	Ph	CO_2Me	Bn	1	96
9	Ph	Ph	CO_2Et	Me	1	97
10	Ph	Ph	CO_2Et	Et	1	96
11	Ph	Ph	CO_2Et	*i*-Bu	1.5	94
12[c]	Ph	Ph	CN	Bn	1.5	81
13[c]	Ph	Ph	H	Bn	1.5	100

[a] The reaction was carried out in dichloromethane (15 mL) at 40 °C under a hydrogen atmosphere (50 atm).
[b] Isolated yield based on the amount of the azabicyclic peroxide **3**. [c] The reaction was carried out in 10% methanol/dichloromethane (15 mL) at 40 °C under a hydrogen atmosphere (50 atm).

carbon and the solvent, only one product was quantitatively obtained (Table 1, Entry 1). The ^1H NMR spectrum of the product showed the three characteristic pairs of the AX system at δ4.48 and 3.62 (J = 14.72 Hz), δ3.50 and 3.45 (J = 10.51 Hz), and δ3.47 and 3.39 (J = 13.52 Hz) assigned to the methylene protons of the benzyl group, pyrrolidone ring, and tetrahydrofuran ring, respectively. In the ^{13}C NMR spectrum, three characteristic *sp*^{3} quaternary carbons were observed at δ 107.6, 90.1, and 67.1, which were assigned to the C-1, C-3, and C-5 carbons, respectively. Although the NMR spectra of the product were very similar to those of the azabicyclic peroxide,[2] the quaternary carbons at C-1, C-3, C-5, and the methylene carbon at C-4 (δ 41.2) in the product were deshielded from 7 to 10 ppm compared to the ^{13}C NMR spectrum of the starting azabicyclic peroxide. Therefore, the structure was assigned to 7-benzyl-5-ethoxycarbonyl-1-hydroxy-3,3-diphenyl-7-aza-2-oxabicyclo[3.3.0]octan-6-one, in addition, the elemental analysis also supported the molecular formula of $C_{28}H_{27}NO_5$. In order to corroborate the exact structure, a single crystal of the product

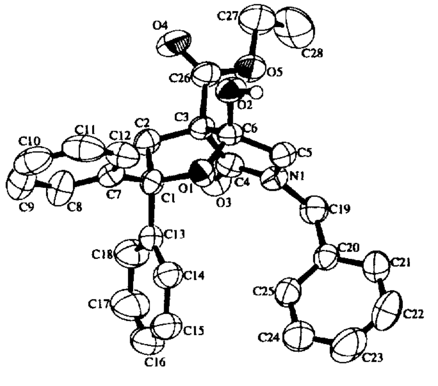

Fig. 1. ORTEP Diagram of **4**
(R^1, R^2 = Ph, R^3 = CO_2Et, R^4 = Bn)

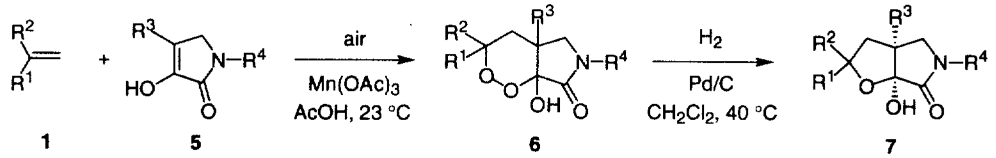

Table 2. Palladium-Catalyzed Reduction of Azabicyclic Peroxides **6** under a Hydrogen Atmosphere[a]

Entry	Azabicyclic peroxide **6**				Reaction time	Reduction product **7**
	R^1	R^2	R^3	R^4	h	yield/%[b]
1	Ph	Ph	CO_2Et	Bn	1	99
2	$4\text{-}MeC_6H_4$	$4\text{-}MeC_6H_4$	CO_2Et	Bn	1	100
3	$4\text{-}MeOC_6H_4$	$4\text{-}MeOC_6H_4$	CO_2Et	Bn	1	99
4[c]	$4\text{-}ClC_6H_4$	$4\text{-}ClC_6H_4$	CO_2Et	Bn	1.3	97
5[c]	$4\text{-}FC_6H_4$	$4\text{-}FC_6H_4$	CO_2Et	Bn	1.5	97
6	Me	Ph	CO_2Et	Bn	1	100
7	Et	Et	CO_2Et	Bn	1.5	100
8	Ph	Ph	CO_2Me	Bn	1	99
9	Ph	Ph	CO_2Bu	Bu	1	94
10	Ph	Ph	CO_2Et	Bu	1	99
11	Ph	Ph	CO_2Et	Et	1	99
12	Ph	Ph	CO_2Bu	Me	1	91
13[c]	Ph	Ph	CN	Bn	2	77

[a] The reaction was carried out in dichloromethane (15 mL) at 40 ℃ under a hydrogen atmosphere (50 atm).
[b] Isolated yield based on the amount of the azabicyclic peroxide **6**. [c] The reaction was carried out in 10% methanol/dichloromethane (15 mL) at 40 ℃ under a hydrogen atmosphere (50 atm).

was measured by X-ray and the final structure was determined as shown in Figure 1.[7] Accordingly, it was found that a simple reductive cleavage of the peroxyl bond followed by recyclization occurred. A similar reduction of other azabicyclic peroxides **3** gave the corresponding 7-aza-2-oxabicyclo[3.3.0]octan-6-ones **4** in almost quantitative yields (Table 1, Entries 2-13).

As the 1-hydroxy-8-aza-2,3-dioxabicyclo[4.3.0]nonan-9-ones **6** were easily prepared from alkenes **1** and 2,3-pyrrolidinediones **5**,[3] a similar reduction of **6** was examined under the same reaction conditions. After the work-up, 7-aza-2-oxabicyclo[3.3.0]octan-8-one derivatives **7** were obtained in the yields shown in Table 2.[7] Although the yield of **4** and **7** bearing a cyano group in the ring junction was slightly low (Table 1, Entry 12 and Table 2, Entry 13), the hydrogenolysis of the azabicyclic peroxides was quite simple and the azabicyclic compounds, which were the formally extruded ones of the peroxide oxygens, were produced in quantitative yields without any purification.

It is well-known that bicyclic endoperoxides can be readily reduced by thiourea to give 2-ene-1,4-diols.[1c,8] Yoshida et al. also reported that 1-hydroxy-4-methyl-4-phenyl-2,3-dioxabicyclo[4.3.0]nonan-7-one reacted with thiourea in refluxing methanol for 7.5 h to afford a similar tetrahydrofuran derivative, and pointed out that the presence of the hydroxyl group at the C-1 position seemed to be essential for the reduction.[8d] The mechanism for the present reduction could be explained by normal hydrogenolysis[9] and subsequent palladiumassisted intramolecular cyclization.[10]

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7. 7-Benzyl-5-ethoxycarbonyl-1-hydroxy-3,3-diphethyl-7-aza-2-oxabicyclo[3.3.0]octan-6-one (**4**: R^1, R^2 = Ph, $R^3 = CO_2Et$, R^4 = Bn): colorless microcrystals (from CH_2Cl_2/methanol); mp 175 ℃; IR ($CHCl_3$) ν 3600-3139 (OH), 1739 (ester C=O), 1700 (amide C=O), 1264 (ester C-O-C); ^1H NMR ($CDCl_3$) δ 7.43-7.06 (15H, m, arom H), 4.48 (1H, d, J = 14.72 Hz, $\underline{H}$CH-Ph), 4.14 (2H, q, J = 7.17 Hz, O-C$\underline{H}_2$CH$_3$), 3.62 (1H, d, J = 14.72 Hz, $\underline{H}$CH-Ph), 3.59 (1H, s, OH), 3.50 (1H, d, J = 10.51 Hz, H-8), 3.47 (1H, d, J = 13.52 Hz, H-4), 3.45 (1H, d, J = 10.51 Hz, H-8), 3.39 (1H, d, J = 13.52 Hz, H-4), 1.19 (3H, t, J = 7.17 Hz, O-CH$_2$C$\underline{H}_3$); ^{13}C NMR ($CDCl_3$) δ 169.5, 167.3 (C=O), 146.3, 144.1, 135.3 (PhC), 128.6 (2C), 128.4 (2C), 128.1 (2C), 127.9 (2C), 127.6, 127.3, 127.2, 125.5 (2C), 125.4 (2C) (PhH), 107.6 (C-1), 90.1 (C-3), 67.1 (C-5), 62.3, 56.4, 46.2, 41.2 (CH_2), 13.9 (Me). Anal. Calcd for $C_{28}H_{27}NO_5$: C, 73.51; H, 5.95; N, 3.06. Found: C, 73.40; H, 6.31; N, 3.16.
   X-ray crystallographic data: space group *P*bca, orthorhombic, a = 17.240(2), b = 22.490(2), c = 12.636(2) Å, V = 4899.3(9) Å^3, Z = 8, $C_{28}H_{27}NO_5$, F.W. = 457.52, ρ = 1.240 g/cm^3, μ = 0.85 cm^{-1}, F_{000} = 1936.00, λ = 0.71069 Å (MoKα), collection range $38.47<2\theta<41.93°$, total data collected 4308, total variables 416, R = 0.039, R_ω = 0.035.
   It was also observed that the carbons at C-1, C-3, C-4, and C-5 in the tetrahydrofuran part of the other products **4** and **7** were deshielded (~ 13 ppm) in the ^{13}C NMR spectra compared to those of the starting azabicyclic peroxides.
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