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Preliminary Communication

Expedient synthesis of 8-aza-1-hydroxy-2,3-dioxabicyclo[4.3.0]nonan-7-ones using manganese(III)-catalyzed aerobic oxidation

Md. Aminul Haque and Hiroshi Nishino*

Department of Chemistry, Graduate School of Science and Technology, Kumamoto University, Kurokami 2-39-1, Kumamoto 860-8555, Japan

*Corresponding author
e-mail: nishino@sci.kumamoto-u.ac.jp

Abstract

The reaction of 3-alkyl-2,4-pyrrolidinediones with 1,1-diarylethenes in the presence of a catalytic amount of manganese(III) acetate resulted in the aerobic endoperoxidation that produced very stable crystalline 8-aza-1-hydroxy-2,3-dioxabicyclo[4.3.0]nonan-7-ones in high yields.

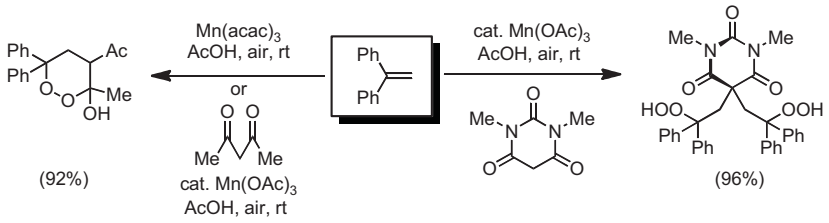
Keywords: catalytic oxidation; endoperoxidation; endoperoxides; manganese(III) acetate; 2,4-pyrrolidinediones.

The oxidation of many organic compounds in air is begun by peroxidation, such as the formation of hydroperoxides and endoperoxides, having a fairly weak oxygen-oxygen bond, and further proceeds to afford the corresponding alcohols, aldehydes, ketones, and/or carboxylic acids (Sheldon and Kochi, 1981; Pryor, 1984; Hudlicky, 1990; Barton et al., 1993). Therefore, when the oxidation involving molecular oxygen is explored, the isolation of the oxidation intermediate, such as peroxides, is important to comprehend the total oxidation process. By contrast, the peroxides are important synthetic targets in organic chemistry because some peroxides are known as a natural product having certain biological activities (Casteel, 1992, 1999). However, it is sometimes difficult to synthesize the peroxides owing to the instability of the oxygen-oxygen bond.

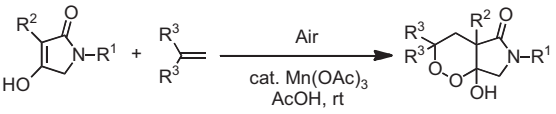
We previously developed the manganese(III)-catalyzed aerobic oxidation reactions using the 1,3-dicarbonyl system, and many functionalized endoperoxides (Nishino, 1985; Tategami et al., 1990; Nishino et al., 1991) and hydroperoxides (Qian et al., 1993) were synthesized (Scheme 1) (Nishino, 2006). In particular, the 1,2-dioxan-3-ols containing the nitrogen heterocycle are important from the viewpoint of pharmacological activity. For example, hydroperoxy pyrazolidinedione derivatives reveal an anti-inflammatory (Reed et al., 1985; Mentz et al., 1987; Vennerstorm and Holmes, 1987) or antimalarial activity (McCullough et al., 1999, 2001; Tokuyasu et al., 2000; Kamata et al., 2002; Griesbeck et al., 2005; Kumar et al., 2009; Barton et al., 2010; Hencken et al., 2010). During the course of our study on the manganese(III)-catalyzed aerobic oxidation, we reported that 2,4-pyrrolidinediones substituted with an electron-withdrawing group at the C-3 position, such as an ester carbonyl group, underwent the formal [2+2+2] cycloaddition of alkenes in air to produce the corresponding endoperoxides (Nguyen et al., 1997, 1998; Chowdhury et al., 1998, 1999; Asahi and Nishino, 2005a,b). Because the pyrrolidinedione analogs have been the focus of a great deal of interest owing to biological activity (Rechenberg, 1962; Chauhan et al., 1999) and because we wanted to know the effect of the substituent on the pyrrolidinedione skeleton, we focused on the aerobic oxidation using the 2,4-pyrrolodinediones bearing an electron-releasing group such as alkyl group substituted at the C-3 reaction position.

3-Alkylsubstituted 2,4-pyrrolidinediones were prepared by the Dieckmann condensation of *N*-alkanoyl-*N*-alkylglycinates which were produced by the reaction of α-bromoacetate with alkylamines followed by alkanoylation with the corresponding alkanoyl chloride (King and McMillan, 1950; Fugger et al., 1955; Speziale and Jaworski, 1960; Koech and Krische, 2004; Zhy et al., 2005). The 2,4-pyrrolidinediones exist as an enol form in an aprotic polar solvent, such as DMSO-d_6 (Chowdhury et al., 1999).

The reaction of 1-benzyl-4-hydroxy-3-methyl-3-pyrrolin-2-one (R^1=Bn, R^2=Me) with 1,1-diphenylethene (R^3=R^4=Ph) was first examined in the presence of a catalytic amount of manganese(III) acetate (Scheme 2). The reaction was carried out as follows. To a solution of 2,4-pyrrolidinedione (1 mmol) and an alkene (0.5 mmol) in glacial acetic acid (25 ml), manganese(III) acetate dehydrate (0.1 mmol) was added. The mixture was stirred at room temperature in air until the alkene was completely consumed, and then the reaction was quenched by adding water (25 ml) to the mixture. The aqueous resulting mixture was extracted three times with dichloromethane (30 ml) and the combined extract was washed with water, a saturated aqueous solution of sodium hydrogen carbonate, dried over anhydrous magnesium sulfate, and then concentrated to dryness. The residue was purified by silica gel column chromatography using ethyl acetate and hexane (50:50 v/v). The reaction was carried out at room temperature in air until the alkene was completely consumed, which did not give our expected 3-(2-hydroperoxyethyl)-2,4-pyrrolidinedione such as in the case of barbituric acid in Scheme 1 but,



Scheme 1



Scheme 2

contrary to our prediction, an azabicyclic endoperoxide in 92% yield (Scheme 2 and Table 1, Entry 1). The product was obtained as stable colorless needles that melted at 210°C. In the IR spectrum, a broad absorption band and a strong absorption band corresponding to a hydroxyl and amide carbonyl group appeared at 3400–3000 cm^{-1} and 1656 cm^{-1}, respectively. The ^{1}H NMR spectrum showed three pairs of geminal AB quartets at δ 4.76 and 3.72 ppm (J=15.0 Hz), δ 3.55 and 2.30 ppm (J=15.0 Hz), δ 3.30 and 2.92 ppm (J=12.0 Hz), which were assigned to benzyl methylenes, dioxane ring methylenes at C-5, and pyrrolinone ring methylenes at C-9, respectively. These methylene protons correlated to the methylene carbons at δ 51.8, 45.4, and 36.6 ppm in the HMQC spectrum. The ^{13}C NMR spectrum revealed three quaternary carbons at δ 100.7 ppm assigned to the C-1 carbon attached to two oxygens, δ 85.7 ppm owing to the C-4 carbon bearing one oxygen, and δ 44.7 ppm assigned to the C-6 ring junction. There spectral data supported not the hydroperoxy but the endoperoxy structure. Because the potassium iodide-starch test of the product showed a negative result and the combustion analysis was consistent with the formula $C_{26}H_{25}NO_4$, the product was determined to be 8-aza-8-benzyl-1-hydroxy-6-methyl-2,3-dioxa-4,4-diphenylbicyclo[4.3.0]nonan-7-one: yield (190.9 mg, 92%); R_f=0.68 (EtOAc:hexane=7:3 v/v); colorless needles (from EtOAc-hexane), m.p. 210°C; IR (KBr) 3400–3100 (OH), 1656 (C=O); ^{1}H NMR ($CDCl_3$) δ 7.67–6.47 (15H, m, arom H), 3.66 (1H, s, OH), 4.76 (1H, d, J=15.0 Hz, $PhCHH_a$), 3.72 (1H, d, J=15.0 Hz, $PhCHH_b$), 3.55 (1H, d, J=15.0 Hz, H_a-5), 3.30 (1H, d, J=12.0 Hz, H_a-9), 2.92 (1H, d, J=12.0 Hz, H_b-9), 2.30 (1H, d, J=15.0 Hz, H_b-5), 1.60 (3H, s, Me); ^{13}C NMR ($CDCl_3$) δ 174.4 (C=O), 145.1, 140.5, 135.2 (arom C), 128.6 (2C), 128.6 (2C), 128.0 (2C), 127.6 (1C), 127.4 (2C), 127.3 (2C), 127.2 (1C), 124.8 (3C) (arom CH), 100.7 (C-1), 85.7 (C-4), 51.8, 45.4, 36.6 (CH_2), 44.7 (C-6), 22.6 (Me). Anal. calcd. for $C_{26}H_{25}NO_4$: C, 75.16; H, 6.06; N, 3.37. Found: C, 75.18; H, 6.12; N, 3.46.

The reaction of other alkyl-substituted 4-hydroxypyrrolinones (R^2=alkyl) was explored under the same aerobic oxidation conditions and the corresponding stable crystalline 2,3-dioxabicyclo[4.3.0]nonan-7-ones were obtained in high yields (Table 1, Entries 2–20). In all cases, the hydroperoxyethyl-substituted 2,4-pyrrolidinediones were not detected and the alkyl-substituted 4-hydroxypyrrolinones (R^2=alkyl) efficiently underwent the endoperoxidation. Surprisingly, a small amount of the 3-hydroperoxy-2,4-pyrrolidinediones was also isolated in some cases (Entries 3, 7, 15, and 16 in Table 1).

1-Benzyl-3-hydroperoxy-3-propylpyrrolidine-2,4-dione: yield (6.7 mg, 5%); R_f=0.54 (EtOAc:hexane=5:5 v/v); colorless solid, m.p. 112°C; IR ($CHCl_3$) 3400–3100 (OOH), 1784, 1693 (C=O); ^{1}H NMR ($CDCl_3$) T_M 11.62 (1H, s, OOH), 7.37–7.27 (5H, m, arom H), 4.76 (1H, d, J=14.4 Hz, CH_2), 4.67 (1H, d, J=14.4 Hz, CH_2), 3.74 (1H, d, J=17.4 Hz, CH_2), 3.64 (1H, d, J=17.4 Hz, CH_2), 1.75 (2H, t, J=8.4 Hz, CH_2), 1.31 (2H, m, CH_2), 0.88 (3H, t, J=7.5 Hz, Me); ^{13}C NMR ($CDCl_3$) T_M 204.8 (C-4, C=O), 171.1 (C-2, C=O), 134.2, 129.1, 128.4, 128.3 (arom C), 85.7 (C-3), 54.1 (C-5, CH_2), 46.8 ($PhCH_2$), 33.5, 15.9 (CH_2), 14.1 (Me). FAB HRMS (acetone/NBA) calcd for $C_{14}H_{17}NO_4Na$ 286.1055 (M+Na). Found 286.1032.

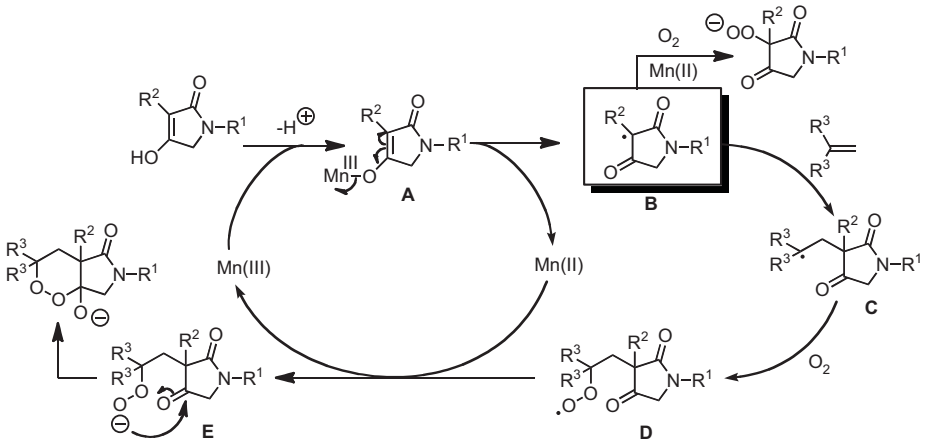
Table 1 Manganese(III)-catalyzed aerobic oxidation of 3-alkyl-2,4-pyrrolidinediones with 1,1-disubstituted alkenes[a].

Entry	Pyrrolidinedione	Alkene	T/h	Product/%[b]
1	R^1=Bn, R^2=Me	R^3=Ph	5	92
2	R^1=Bn, R^2=Et	R^3=Ph	5	85
3	R^1=Bn, R^2=Pr	R^3=Ph	7	89[c]
4	R^1=Bn, R^2=Bu	R^3=Ph	5	84
5	R^1=Et, R^2=Me	R^3=Ph	6.5	89
6	R^1=*i*-Pr, R^2=Me	R^3=Ph	6.5	78
7	R^1=*i*-Pr, R^2=Et	R^3=Ph	7	75[c]
8	R^1=*i*-Pr, R^2=Pr	R^3=Ph	7	81
9	R^1=*i*-Pr, R^2=Bu	R^3=Ph	7.5	77
10	R^1=Bu, R^2=Me	R^3=Ph	5	91
11	R^1=Bu, R^2=Et	R^3=Ph	5	88
12	R^1=Bu, R^2=Pr	R^3=Ph	5	85
13	R^1=Bu, R^2=Bu	R^3=Ph	7	77
14	R^1=*t*-Bu, R^2=Me	R^3=Ph	7	93
15	R^1=*t*-Bu, R^2=Pr	R^3=Ph	5.5	85[c]
16	R^1=*t*-Bu, R^2=Bu	R^3=Ph	6.5	81[c]
17	R^1=Bn, R^2=Me	R^3=4-MeC_6H_4	5	82
18	R^1=Bn, R^2=Me	R^3=4-$MeOC_6H_4$	5	82
19	R^1=Bn, R^2=Me	R^3=4-ClC_6H_4	7	75
20	R^1=Bn, R^2=Me	R^3=4-FC_6H_4	7	71

[a]The reaction of 2,4-pyrrolidinediones (1 mmol) with alkenes (0.5 mmol) was carried out in acetic acid (25 ml) at ambient temperature in air in the presence of manganese(III) acetate (0.1 mmol).

[b]The yield is based on the alkene used.

[c]A small amount of the corresponding 3-hydroperoxy-2,4-pyrrolidinedione was also isolated.



Scheme 3

The formation of the endoperoxides deserves comment. Because the alkyl group was substituted at the C-3 position of the 2,4-pyrrolidinedione, the formation of the manganese(III)-enolate complex **A** should be slow (Snider, 2009), and subsequent single-electron transfer oxidation by manganese(III) resulted in the pyrrolidinedione radicals **B** which must be stabilized by the alkyl substituent. Therefore, the radical **B** had a chance to be trapped by the added alkene or a small amount of dissolved molecular oxygen in the solvent. When the radical **B** was captured by the alkene, the more stable tertiary radicals **C** would be produced and subsequent molecular oxygen trapping would afford the peroxy radicals **D**. The peroxy radical **D** is subject to a single-electron transfer reduction by manganese(II) species, giving the peroxy anions **E**. Because the keto carbonyl group of the pyrrolidinedione is more sufficiently electrophilic than that of the amide carbonyl group, the peroxy anion **E** must be cyclized to finally give the hydroxyl endoperoxides after work-up. By contrast, when the pyrrolidinedione radical **B** was scavenged by the dissolved molecular oxygen, the 3-hydroperoxy-2,4-pyrrolidinediones should be directly formed as a byproduct. However, the excess amount of the pyrrolidinediones might also somewhat undergo direct hydroperoxidation after consumption of the added alkene. The reaction pathway is outlined in Scheme 3.

In summary, we have demonstrated that the convenient endoperoxidation of several 3-alkyl-substituted 2,4-pyrrolidinediones produced 8-aza-1-hydroxy-2,3-dioxabicyclo[4.3.0] nonan-7-ones under the manganese(III)-catalyzed aerobic oxidation conditions. Although the results were similar to those of the reaction using the 2,4-pyrrolidinedione-3-carboxylates, the reaction time was much shorter than that of the reaction using 2,4-pyrrolidinedione-3-carboxylates (Chowdhury et al., 1999). Furthermore, to achieve the high yield of the endoperoxides, using a catalytic amount of manganese(III) acetate (0.1 equivalent) was sufficient to complete the former reaction (Chowdhury et al., 1999). A further study of the biological screening, such as the antibacterial and herbicidal activities of the endoperoxides, is currently underway.

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