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One-Pot Synthesis of Azabicyclic Peroxides from Tetramic Acid Derivatives by Manganese(III)-Mediated Oxidative [2+2+2] Cycloaddition

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Abstract: A simple azabicyclic peroxide synthesis was achieved by the manganese(III)-mediated oxidative formal [2+2+2] cycloaddition. A mixture of tetramic acid derivatives and alkenes was oxidized with manganese(III) acetate under a dry air stream to give 1-hydroxy-8-aza-2,3-dioxabicyclo[4.3.0]nonan-7-ones in good to quantitative chemical yields.

Keywords: Azabicyclic peroxides; Tetramic acid derivatives; Manganese(III) acetate; Oxidation

Tetramic acid derivatives are widely found as a metabolic product and some have various biological activities.[1] Naturally occurring bicyclic peroxides are also known as a plant growth regulator[2] and antimalarial agents.[3] In order to synthesize much more biologically effective compounds, we applied tetramic acid derivatives to bicyclic peroxide synthesis using manganese(III) acetate.[4] Tetramic acid is a tautomer of 2,4-pyrrolidinedione[5] which is a cyclic 1,3-dicarbonyl compound, and it could be an effective candidate to form carbon radicals during the manganese(III) acetate oxidation.[6] In connection with our previous study, we achieved the synthesis of bicyclic peroxides containing both a 1,2-dioxane ring and a lactam ring during the manganese(III)-based formal [2+2+2] cycloaddition of molecular oxygen, alkenes, and 2,3-pyrrolidinediones bearing an electron-withdrawing substituent at the 4-position.[7] This prompted us to use tetramic acid derivatives in the manganese(III)-based formal [2+2+2] cycloaddition to synthesize azabicyclic peroxides. In this communication, we briefly describe the results of our study.

Tetramic acid derivatives **1** were prepared by the condensation of *N*-substituted glycinates and malonic acid monoesters followed by cyclization in the presence of sodium ethoxide.[8] To a mixture of ethyl 1-benzyl-4-hydroxy-3-pyrrolin-2-one-3-carboxylate **1** (R^1 = CO_2Et, R^2 = Bn) (261 mg) and manganese(III) acetate (135 mg) in acetic acid (30 mL), gaseous 2-methylpropene **2** (R^3, R^4 = Me, R^5 = H) and dry air were slowly bubbled. The reaction was monitored by TLC and the pyrrolidinedione **1** was consumed after 5 h. Water (30 mL) was then added to the reaction mixture, followed by extraction with methylene chloride and separation by preparative silica gel TLC developing with 2% methanol-chloroform, which gave the crystalline product **3** (R^1 = CO_2Et, R^2 = Bn, R^3, R^4 = Me, R^5 = H) in 77% yield (Table 1, Entry 1). The structure of **3** (R^1 = CO_2Et, R^2 = Bn, R^3, R^4

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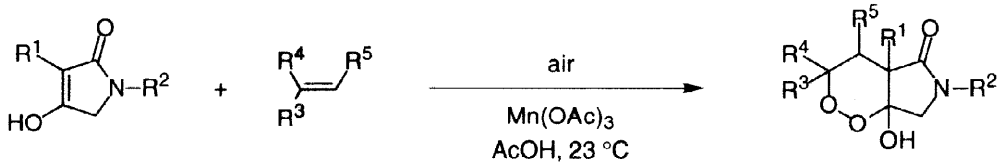


1 2 3

Table 1. Reaction of Tetramic Acids **1** with Alkenes **2** in the Presence of Manganese(III) Acetate under Air[a]

Entry	Tetramic acid **1**		Alkene **2**			Molar ratio[b]	Time	Azabicyclic peroxide **3**
	R^1	R^2	R^3	R^4	R^5		h	yield/%[c]
1	CO_2Et	Bn	Me	Me	H	2:excess:1[d]	5	77
2	CO_2Et	Bn	Et	Et	H	1:3:1	12	58
3	CO_2Et	Bn	H	R^4-R^5 = -$(CH_2)_6$-		1:3:1	16	24
4	CO_2Et	Bn	Ph	Ph	H	2:1:1	14	93
5	CO_2Et	Bn	4-MeC_6H_4	4-MeC_6H_4	H	2:1:1	14	98
6	CO_2Et	Bn	4-ClC_6H_4	4-ClC_6H_4	H	2:1:1	12	89
7	CO_2Et	Bu	Ph	Ph	H	2:1:1	12	83
8	CO_2Et	*iso*-Bu	Ph	Ph	H	2:1:1	12	79
9	CO_2Et	Et	Ph	Ph	H	2:1:1	12	83
10	CO_2Et	Me	Ph	Ph	H	2:1:1	12	88
11	CO_2Et	H	Ph	Ph	H	2:1:1	12	73
12	CO_2Me	H	Ph	Ph	H	2:1:1	14	75
13	CO_2Me	Bn	Ph	Ph	H	2:1:1	12	74
14	CN	Bn	Ph	Ph	H	2:1:1	12	84
15	CN	Bu	Ph	Ph	H	2:1:1	5	88
16	H	Bn	Me	Me	H	2:excess:1[d]	1	51
17	H	Bn	Ph	Ph	H	2:1:1	3	70

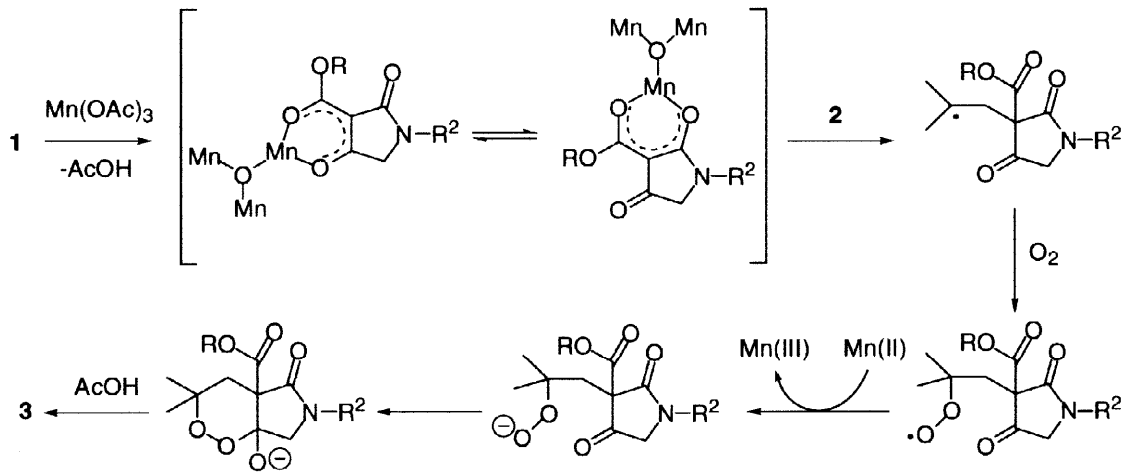
[a] The reaction was carried out in acetic acid (30 mL) at 23 ℃ under a dry air stream.
[b] The molar ratio is revealed as tetramic acid **1**:alkene **2**:manganese(III) acetate.
[c] Isolated yield based on the amount of the alkene **2** used except for entries 1-3 and 16 in which the yields were calculated on the basis of the tetramic acid **1**.
[d] 2-Methylpropene was bubbled into the reaction mixture.

= Me, R^5 = H) was established by spectroscopic methods and elemental analysis. The ^1H NMR spectrum showed the three characteristic pairs of the AX system at δ 4.75 and 4.33 (J = 14.8 Hz), δ 3.57 and 3.14 (J = 10.8 Hz), and δ 2.50 and 2.23 (J = 14.3 Hz) assigned to the methylene protons of the benzyl group, pyrrolinone ring, and dioxane ring, respectively, together with peaks due to a phenyl (δ 7.28), a hydroxyl (δ 5.06 which disappeared upon deuteration), an ethoxyl (δ 4.11 and 1.11), and two methyl groups (δ 1.26 and 1.22). In the ^{13}C NMR spectrum, ester and amide carbonyl carbons appeared at δ 170.4 and 167.8, and three characteristic sp^3 quaternary carbons were observed at δ 100.2, 77.6, and 56.4, which were assigned to the C-1, C-4, and C-6 carbons, respectively. Accordingly, the structure of **3** was deduced to be 8-benzyl-6-ethoxycarbonyl-1-hydroxy-4,4-dimethyl-8-aza-2,3-dioxabicyclo[4.3.0]nonan-7-one based on these spectral data and, in addition, the elemental analysis supported the molecular formula of $C_{18}H_{23}NO_6$.[9,10] The stereochemistry of the ring junction of C-1 and C-6 has not been determined, however, from the molecular modeling study, it could be assumed that a *cis*-fused bicyclic peroxide was more stable than the *trans*-isomer.[11] 2-Ethyl-1-butene and cyclooctene were also conducted under similar reaction conditions to give the corresponding azabicyclic

peroxides **3** (Entries 2 and 3). Similar reactions were examined under various reaction conditions, and as a result, the best yield of the azabicyclic peroxides **3** was achieved using 1,1-diarylethenes at the molar ratio of **1**:**2**:$Mn(OAc)_3$ = 2:1:1 (Entries 4-6). Furthermore, it was found that the use of *N*-deprotected 2,4-pyrrolidinediones decreased the yields of **3** (Entries 11 and 12) since the amido hydrogen might be sensitive to the manganese oxidant under these conditions.[12]

The Mn(III)-2,4-pyrrolidinedione enolate complex should be formed during the first stage similar to the La(III), Sm(III), Eu(III), and Gd(III)-enolate complexes[13] and the subsequent one-electron transfer took place to give the corresponding 2,4-pyrrolidinedione radicals which simultaneously attacked the alkene **2** to yield tertiary or secondary carbon radicals as shown in Scheme 1. The molecular oxygen in bubbled air then reacted with the carbon radicals to give peroxy radicals which were reduced by Mn(II) species followed by cyclization to give the final products **3**. Therefore, the Mn(III) species were regenerated in this system, that is, Mn(III) functioned as a catalyst.[14] However, two equivalents of 2,4-pyrrolidinedione **1** against 1,1-diarylethene **2** were employed so that 2,4-pyrrolidinedione itself was also oxidatively decomposed by the manganese(III) acetate.

Scheme 1



A similar reaction of 3-cyano-4-hydroxy-3-pyrrolin-2-ones with 1,1-diphenylethene gave the corresponding azabicyclic peroxides probably in a similar manner (Entries 14 and 15).[15] 1-Benzyl-2,4-pyrrolidinedione, which is present in the keto form in the solution, also reacted with gaseous 2-methylpropene and 1,1-diphenylethene to afford the corresponding azabicyclic peroxides (Entries 16 and 17).

In order to synthesize the 3-aza-6-oxabicyclo[3.3.0]octan-2-one skeleton, the manganese(III) oxidation of a mixture of the tetramic acid derivative **1** (R^1 = CO_2Et, R^2 = Bn) and alkene **2** (R^3, R^4 = Ph, R^5 = H) was examined in *boiling* acetic acid under *an argon atmosphere*. However, our attempt failed and only the 3-substituted 2,4-pyrrolidinediones were obtained.[7,12b,c]

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9. 8-Benzyl-6-ethoxycarbonyl-1-hydroxy-4,4-dimethyl-8-aza-2,3-dioxabicyclo[4.3.0]nonan-7-one (**3**: R^1 = CO_2Et, R^2 = Bn, R^3, R^4 = Me, R^5 = H): colorless microcrystals (from CH_2Cl_2/hexane); mp 153 ℃; IR ($CHCl_3$) ν 3563, 3500-3100 (OH), 1740 (ester C=O), 1701 (amide C=O), 1252 (ester C-O-C); ^{1}H NMR ($CDCl_3$) δ 7.28 (5H, m, Ph), 5.06 (1H, s, OH), 4.75 (1H, d, J = 14.8 Hz, HCH-Ph), 4.33 (1H, d, J = 14.8 Hz, HCH-Ph), 4.11 (2H, q, J = 7.2 Hz, O-CH_2CH_3), 3.57 (1H, d, J = 10.8 Hz, H-9), 3.14 (1H, d, J = 10.8 Hz, H-9), 2.50 (1H, d, J = 14.3 Hz, H-5), 2.33 (1H, d, J = 14.3 Hz, H-5), 1.26 (3H, s, CH_3), 1.22 (3H, s, CH_3), 1.11 (3H, t, J = 7.2 Hz, O-CH_2CH_3); ^{13}C NMR ($CDCl_3$) δ 170.4 (ester C=O), 167.8 (amide C=O), 135.1 (PhC), 128.7 (PhH), 128.3 (PhH), 127.8 (PhH), 100.2 (C-1), 77.6 (C-4), 62.3 (OCH_2CH_3), 56.4 (C-6), 54.0 (PhCH_2), 46.9 (C-9), 32.4 (C-5), 27.9 (CH_3), 23.6 (CH_3), 13.8 (OCH_2CH_3).
Anal. Calcd for $C_{18}H_{23}NO_6$: C, 61.88; H, 6.64; N, 4.01. Found: C, 61.90; H, 6.73; N, 4.02.
10. Reduction of the cyclic peroxide **3** (R^1 = CO_2Et, R^2 = Bn, R^3, R^4 = Ph, R^5 = H), which was suggested by one of the referees was carried out under a hydrogen atmosphere (50 atm) in the presence of palladium charcoal in methylene chloride at 40 ℃ for 1 h, quantitatively gave the 3-benzyl-1-ethoxycarbonyl-5-hydroxy-7,7-diphenyl-3-aza-6-oxabicyclo[3.3.0]octan-2-one.
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