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Manganese(III)-Catalyzed Facile Direct Hydroperoxidation of Some Heterocyclic 1,3-Dicarbonyl Compounds

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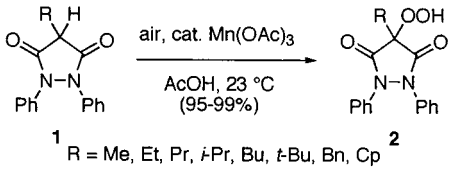
ABSTRACT



The aerobic oxidation of 4-monosubstituted 1,2-diphenylpyrazolidine-3,5-diones 1 was carried out in the presence of a catalytic amount of manganese(III) acetate to quantitatively give the corresponding 4-hydroperoxypyrazolidinediones 2. A similar autoxidation of the 5-monosubstituted barbituric acids 5 and 3-butyl-4-hydroxy-2-quinolinone 7 also gave the corresponding hydroperoxides 5 and 8, respectively, in moderate to excellent yields.

4-Butyl-1,2-diphenylpyrazolidine-3,5-dione (phenylbutazone **I**), a nonsteroidal antiinflammatory drug, is an efficient reducing cofactor for the peroxidase activity of prostaglandin H synthase.[1] Phenylbutazone **I** inhibits the production of lipid mediators causing inflammation but paradoxically performs this via the intermediacy of the peroxyl radical and hydroperoxide, which may themselves be proinflammatory. In isolated heart preparations of guinea pigs and rabbit hearts in vivo, 4-butyl-4-hydroperoxy-1,2-diphenylpyrazolidine-3,5-dione (**II**) shows a significantly stronger cardiodepressive and coronary constricting effect compared to phenylbutazone **I** itself, 4-butyl-4-hydroxy-1,2-diphenylpyrazolidine-3,5-dione (**III**), and the ring-opened decomposition product of the hydroperoxide **II**.[2] These phenomena could shed light on the significance of the hydroperoxylated phenylbutazone **II** regarding the antiinflammatory or other biological activities of phenylbutazone **I**, e.g., rheumatoid arthritis,[3] and could explain the side effects such as gastric irritation and toxicity associated with phenylbutazone **I**. A number of reagents have been utilized for the introduction of an oxygen functionality at the 2-position of the 1,3-dicarbonyl compounds, e.g., lead(IV) acetate,[4] MoOPH,[5] percarboxylic acids,[6] dimethyldioxirane,[7] manganese(II) acetate,[8] cerium(III) chloride,[9] cobalt(II) chloride,[10] ammonium cerium(IV) nitrate (CAN),[11] and cesium salts.[12] However, in all of these cases, only the

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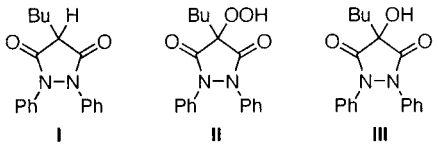
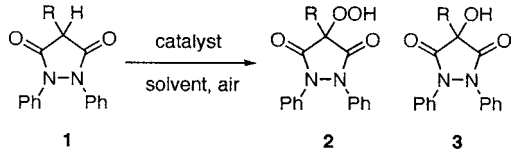
hydroxyl functionality could be introduced at the 2-position of the 1,3-dicarbonyl compounds.



I II III

During the course of our current investigation of the manganese(III) acetate-catalyzed oxidative functionalization of pyrazolidine-3,5-diones to synthesize a variety of derivatives with potent biological activity, we found that stirring a 1 mM solution of different 4-monoalkylpyrazolidine-3,5-diones **1** (R = Me, Et, Pr, *i*-Pr, Bu, *t*-Bu, Bn, and cyclopentyl) in acetic acid in the presence of a catalytic amount of manganese(III) acetate under an aerobic atmosphere gave the hydroperoxylated products **2** in quantitative yields (Scheme 1 and Table 1, entries 2−10).[13]

Scheme 1



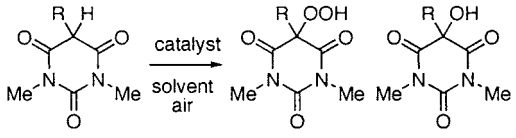
1 **2** **3**

When no catalyst was used, there was no conversion of **1** to **2** (entry 1), which implies that manganese(III) acetate is essential for the catalytic hydroperoxidation. All the products **2** in dichloromethane showed a positive potassium iodide-starch test. The structural assignment of **2** was based on the ^{1}H NMR, ^{13}C NMR, and IR spectra and finally X-ray crystallography.

When these autoxidation reactions were carried out for a longer reaction period in acetic acid or ethanol with a catalytic amount of manganese(III) acetate or utilizing CAN, a substantial amount of the hydroxylated pyrazolidinediones **3** was formed (entries 11−14). Copper(II) acetate as the catalyst was not effective for the autoxidation (entry 15). In addition, the formed hydroperoxides **2** were stable in sunlight or visible light,[14] and the reduction of **2** (R = Me, Et, Pr, *i*-Pr) with triphenylphosphine in diethyl ether gave the corresponding **3** in 97, 98, 97, and 96% yields, respectively.

To examine the applicability of the manganese(III) acetate-catalyzed α-hydroperoxidation of other biologically important heterocyclic 1,3-dicarbonyl compounds, the reaction of 5-monosubstituted barbituric acids **4** (R = Bn, *i*-Pr, 4-$MeOC_6H_4CH_2$, 2-$MeOC_6H_4CH_2$, 2-naphthyl-CH_2)[15] and 3-butyl-4-hydroxy-2-quinolinone **7**[16] was carried out under similar aerobic conditions, and very similar autoxidation results were obtained, giving the corresponding hydroperoxides **5** (Scheme 2 and Table 2) and **8** (Scheme 3), respectively, in excellent

Scheme 2



4 **5** **6**

or moderate yields. All of the compounds **5** and **8** also tested positive for the hydroperoxyl group using the potassium iodide-starch paper.

In the case of the barbituric acids **4**, stirring for a long reaction time or using CAN as the catalyst also led to the formation of hydroxybarbituric acids **6** (Table 2, entries

Table 1. Aerobic Oxidation of 4-Alkyl-1,2-diphenylpyrazolidine-3,5-diones **1** in the Presence of a Catalyst[a]

							yield (%)[b]	
entry	R group of **1**	catalyst	**1**:catalyst	solvent	temp (°C)	time (h)	**2**	**3**
1	*i*-Pr	none		AcOH	23	3	recovery of **1** (100)	
2	*i*-Pr	$Mn(OAc)_3$	1:0.1	AcOH	23	2	97	
3[c]	*i*-Pr	$Mn(OAc)_3$	1:0.1	AcOH	23	2	96	
4	Me	$Mn(OAc)_3$	1:0.1	AcOH	23	2	95	
5	Et	$Mn(OAc)_3$	1:0.1	AcOH	23	2	95	
6	Pr	$Mn(OAc)_3$	1:0.1	AcOH	23	2	99	
7	Bu	$Mn(OAc)_3$	1:0.1	AcOH	23	2	99	
8	*t*-Bu	$Mn(OAc)_3$	1:0.1	AcOH	23	10 min	95	
9	Bn	$Mn(OAc)_3$	1:0.1	AcOH	23	2	97	
10	Cp[d]	$Mn(OAc)_3$	1:0.1	AcOH	23	2	99	
11	*i*-Pr	$Mn(OAc)_3$	1:0.1	AcOH	23	12	87	8
12	*i*-Pr	$Mn(OAc)_3$	1:0.2	AcOH	23	27	52	46
13	*i*-Pr	$Mn(OAc)_3$	1:0.28	EtOH	23	3	54	41
14	*i*-Pr	CAN[e]	1:1	MeOH	0	1	35	55
15	*i*-Pr	$Cu(OAc)_2$	1:0.2	AcOH	23	15	recovery of **1** (94)	

[a] Reaction of **1** (1 mmol) was carried out in air. [b] Isolated yield based on the pyrazolidinedione **1** used. [c] Reaction was carried out in the dark. [d] Cp = cyclopentyl. [e] Ammonium cerium(IV) nitrate.

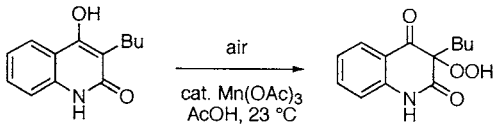
Table 2. Manganese(III)-Catalyzed Oxidation of the 5-Substituted 1,3-Dimethylbarbituric Acids **4**[a]

entry	R group of **4**	time (h)	yield (%)[b] **5**	**6**
1	Bn	2	90	
2	Bn	3	88	7
3	Bn	5	79	18
4	Bn	18	78	15
5[c]	Bn	30 min	47	43
6	*i*-Pr	4	80	
7	4-$MeOC_6H_4CH_2$	4	94	
8	2-$MeOC_6H_4CH_2$	4	94	
9	2-naphthyl-CH_2	2	88	

[a] Reaction was carried out in glacial acetic acid (30 mL) at 23 °C in air at the molar ratio of **4** (1 mmol):$Mn(OAc)_3$ = 1:0.1. [b] Isolated yield based on **4** used. [c] Reaction with CAN was conducted in methanol (30 mL) at 0 °C at the molar ratio of **4** (1 mmol):CAN = 1:1.

2−5). Furthermore, the hydroperoxide **5** (R = Bn) was deoxygenated with triphenylphosphine in diethyl ether to give the corresponding **6** in 80% yield.

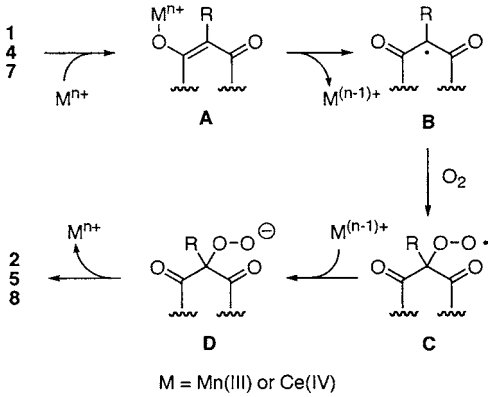
Scheme 3



7 **8** (57%)

To rationalize our experimental result, we presumed that the formation of the Mn(III)−enolate or Ce(IV)−enolate complex **A** in situ undergoing a one-electron transfer to give the 1,3-dicarbonyl radical **B** and the reduced metal ions (Scheme 4).[9,17] The 1,3-dicarbonyl radical **B** could be trapped by dissolved molecular oxygen in the solution to give the peroxyl radical **C**.[18] This radical **C** could either (1) take up a hydrogen atom from another substrate molecule[19] or solvent or (2) be reduced by Mn(II)[17a,b] or Ce(III)[9] to give the corresponding hydroperoxyl anion **D**, which would be subsequently protonated to give the products **2**, **5**, and **8**.

Scheme 4



M = Mn(III) or Ce(IV)

Since the second process would regenerate the catalyst and it is well-known that metal ions, e.g., Cu(I) or Co(II), can reduce the peroxyl radical to the corresponding anion,[20] we assumed that a similar reduction could be possible with Mn(II) or Ce(III). Therefore, path 2 is probably the major route to the product. Involvement of the peroxyl radicals, as well as the hydroperoxide intermediates, during the transition metal-catalyzed autoxidation of different 1,3-dicarbonyl compounds has been already proposed;[11,18] however, there is only one report on the detection and identification of such peroxyl radicals by the electron spin resonance measurement.[18d] To the best of our knowledge, there is no report on the isolation and characterization of 2-hydroperoxy-1,3-dicarbonyl compounds via the transition metal-catalyzed autoxidation. The formation of hydroxyl derivatives **3** and **6** can be attributed to the decomposition of the corresponding hydroperoxides **2** and **5**. We scrutinized several decomposition reactions of **2** and **5** under different reaction conditions (Table 3). As a result, we determined that the decomposition of **2** and **5** is neither thermal[21] (Table 3, entry 1) nor photochemical[14] (Table 3, entry 3) in nature; instead, hydroperoxides **2** and **5** are decomposed to the corresponding alcohols **3** and **6** by the redox reaction of the Mn(III)/Mn(II)

Table 3. Metal Ion-Mediated Decomposition of Hydroperoxides **2** and **5**[a]

entry	ROOH	catalyst	ROOH: catalyst	time, h	ROH (%)[b]	recovered ROOH (%)
1	**2**[c]	none		23		**2** (100)
2	**2**[c]	$Mn(OAc)_3$	1:0.1	23	**3** (47)	**2** (32)
3[d]	**2**[c]	$Mn(OAc)_3$	1:0.1	23	**3** (47)	**2** (33)
4[e]	**2**[c]	$Mn(OAc)_2$	1:1	14	**3** (25)	**2** (66)
5[f]	**2**[c]	CAN	1:1	2	**3** (47)	**2** (33)
6	**5**[g]	$Mn(OAc)_3$	1:0.4	23	**6** (40)	**5** (50)

[a] Reaction of **2** and **5** (1 mmol) was carried out at 23 °C in glacial acetic acid (30 mL) in air except for entry 5. [b] Isolated yield based on the hydroperoxide used. [c] R = *i*-Pr. [d] Reaction was conducted in the dark. [e] Reaction was carried out under an argon atmosphere. [f] Reaction of **2** (1 mmol) was carried out at 0 °C in methanol (30 mL) in air. [g] R = Bn.

(13) Reaction was quenched by adding water, and extraction with dichloromethane, followed by silica gel column chromatographic separation, gave **2**.

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and Ce(IV)/Ce(III) couples, which is typical for the decomposition of alkylhydroperoxides by manganese and cobalt ions.[22]

In summary, we have demonstrated for the first time that the manganese(III)-catalyzed autoxidation of heterocyclic 1,3-dicarbonyl compounds provided the corresponding hydroperoxides in excellent yields. 4-Benzyl-4-hydroperoxy-1,2-diphenylpyrazolidine-3,5-dione (**2**, R = Bn) showed a weak antimalarial activity.[23]

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(23) Antimalarial test was performed at the Laboratory of Drug Informatics, Faculty of Pharmaceutical Science, Okayama University, Japan.

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Supporting Information Available: Experimental procedures and full characterization for compound **2** (R = Bn) including a selected X-ray data. This material is available free of charge via the Internet at http://pubs.acs.org.

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