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SYNTHESIS SOME NEW 8-AZA-2,3-DIOXABICYCLO[4.3.0]NONANE DERIVATIVES BY MANGANESE(III)-CATALYZED REACTION

Le Thi My Trinh, Nguyen Van Ha*

Department of Chemistry, Dalat University, 1 Phu Dong Thien Vuong, Dalat, Vietnam

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Abstract

Some new 8-aza-2,3-dioxabicyclo[4.3.0]nonane derivatives bearing different substituents at the 4-position were synthesized in high yields. This was done by using the reaction of 1,1-disubstituted ethenes with methyl 1-benzyl-2,3-pyrrolidinedione-4-carboxylate in the presence of manganese triacetate dihydrate as a catalyst. The spectrometric features and the reaction mechanism are discussed.

Keywords. Oxygen molecule trapping reaction, 8-aza-2,3-dioxabicyclo[4.3.0]nonanes, manganese(III) catalyst.

1. INTRODUCTION

Manganese triacetate dihydrate is well known as an oxidizing agent in organic synthesis. It belongs to a group of so-called one electron oxidants. Thus, a reaction which oxidized by manganese triacetate dihydrate involves two oxidative steps. The first step produces a radical and the second one is to give a carbocation [1]. However, as a matter of fact, this agent can play a catalytic role in a kind of reaction called oxygen molecular trapping reaction and has been applied well in the synthesis of peroxides, especially 1,2-dioxane-3-ol derivatives [2]. These compounds are of interest because their 1,2-dioxane moiety is present in many natural products and some of them exhibit significant biological activities [3]. We have successfully employed manganese triacetate dihydrate as a catalyst for the synthesis of endoperoxide containing a cyano group [4], and bicyclic endoperoxides bearing nitrogen atom [5]. In an effort to expand the scope of the manganese(III) catalytic cyclization to include direct access to 8-aza-2,3-dioxabicyclo[4.3.0]nonan-9-ones possessing different substituents at the 4-position, we prepared five 1,1-disubstituted alkenes and examined reactions of these compounds with methyl 1-benzyl-2,3-pyrrolidinedione-4-carboxylate in the presence of manganese triacetate dihydrate as a catalyst. In this paper our results concerning that work is reported.

2. EXPERIMENTAL

2.1. Measurements

All of the ^{1}H and ^{13}C NMR spectra were recorded with a Bruker Avance 500 FT NMR spectrometer at 500 MHz for ^{1}H and 125 MHz for ^{13}C, respectively, with tetramethylsilane as the internal standard. The chemical shifts are shown in δ values (ppm) and coupling constants in Hz. The IR spectra were measured on a Jasco FT IR 4100 Spectrometer and the IR spectral data are expressed in cm^{-1} (ν). Mass spectra were recorded with an Agilent GC MS 7895A. The melting points were determined with a Gallenkamp, Sanyo melting point apparatus.

2.2. Materials

Manganese(III) acetate dihydrate, $Mn(OAc)_3{\cdot}2H_2O$, was prepared according to the literature method [6]. 1,1-Disubstituted ethenes **1a-f** were prepared by dehydration of the corresponding alcohols, which were synthesized from substituted acetophenones and arylmagnesium bromides [7]. Methyl 1-benzyl-2,3-pyrrolidinedione-4-carboxylate was prepared by treatment of methyl (β-benzylamino)propionate [8] with dimethyl oxalate in the presence of sodium methoxide according to the procedure used for methyl 1-phenyl-2,3-pyrrolidinedione-4-carboxyxlate [9]. Manganese(II) acetate tetrahydrate, benzylamine, dimethyl oxalate, and methyl acrylate were purchased from Wako

Pure Chemical Ind., Ltd., glacial acetic acid from Sigma-Aldrich Corp. and were used as received.

2.3. Reaction procedure

A typical procedure is as follows. 1,1-Disubstituted ethene (0.25 mmol) was weighed into a 30 mL flask equipped with a magnetic stirrer. Glacial acetic acid (10 mL), methyl 1-benzyl-2,3-pyrrolidinedione-4-carboxylate (0.5 mmol), and manganese (III) acetate dihydrate (0.25 mmol) were added. The mixture was openly stirred at 23 ^{o}C under the air for 12 hours. The solvent was removed *in vacuo*, and the residue was quenched with water. The aqueous mixture was extracted three times with chloroform. The combined extract was dried over anhydrous sodium sulfate, filtered and concentrated to dryness. The products were separated on silica gel TLC (Merck Kieselgel 60 F_{254}) with methanol/chloroform (1:99 v/v) as the developing solvent.

2.4. Product data

*8-Benzyl-1-hydroxy-6-methoxycarbonyl-4,4-bis(4-methylphenyl)-8-aza-2,3-dioxabicyclo[4.3.0]nonan-9-one (***3a***):* colorless crystal, mp 174^{o}C; IR (cm^{-1}) 3405 (broad, OH), 1720, 1710 (COO, CON); ^{1}H NMR ($CDCl_3$, δ, ppm) 7.30-6.97 (13H, m, arom H), 4.53 (1H, d, *J* = 15, –CH$\underline{H}^{a}$Ph), 4.26 (1H, d, *J* = 15, –CH$\underline{H}^{b}$Ph), 3.60 (3H, s, –OCH_3), 3.36 (1H, d, *J* = 15, C7-$\underline{H}^{a}$), 3.02 (2H, s, C-5H_2), 2,78 (1H, d, *J* = 15, C-7$\underline{H}^{b}$), 2.30 (3H, s, –CH_3), 2.27 (3H, s, –CH_3; ^{13}C NMR ($CDCl_3$, δ, ppm) 171.57 (–COO–), 166.28 (C-9), 141.20, 139.11, 137.88, 136.86, 134.40 (arom C), 129.14 (2C), 129.07 (2C), 128.60 (2C), 127.87 (2C), 127.58, 126.02 (2C), 125.94 (2C) (arom CH), 99.72 (C-1), 84.32 (C-4), 52.84 (–OCH_3), 49.26(1H, d, *J* = 15, C7-$\underline{H}^{a}$) (–C$\underline{H}_2$Ph), 47.20 (C-7), 47.08 (C-6), 33.40 (C-5), 29.73, 21.06, 21.00 (CH_3).

*8-Benzyl-1-hydroxy-6-methoxycarbonyl-4-(4-methylphenyl)-4-phenyl-8-aza-2,3-dioxabicyclo[4.3.0]nonan-9-one (***3b***):* colorless crystal, mp 164^{o}C; IR (cm^{-1}) 3320 (broad, OH), 1740, 1715 (COO, CON).

*8-Benzyl-4,4-bis(4-chlorophenyl)-1-hydroxy-6-methoxycarbonyl-8-aza-2,3-dioxabicyclo[4.3.0]nonan-9-one (***3c***):* colorless crystal, mp 172^{o}C; IR (cm^{-1}) 3259 (broad, OH), 1730, 1702 (COO, CON); ^{1}H NMR ($CDCl_3$, δ, ppm) 7.33-6.96 (13H, m, arom H), 4.62 (1H, d, *J* = 14.5, –CH$\underline{H}^{a}$Ph), 4.16 (1H, d, *J* = 14.5, –CH$\underline{H}^{b}$Ph), 3.67 (3H, s, –OCH_3), 3.33 (1H, d, *J* = 15, C7-$\underline{H}^{a}$), 3.06 (1H, d, *J* = 11, C5-$\underline{H}^{a}$), 2.90 (1H, d, *J* = 11, C5-$\underline{H}^{b}$), 141.30, 140.40, 134.07, 133.69 (arom C), 128.84 2,75 (1H, d, *J* = 15, C-7$\underline{H}^{b}$); ^{13}C NMR ($CDCl_3$, δ, ppm) 171.13 (–COO–), 168.80 (C-9), 142.50, (2C), 128.76 (4C), 127.99, 127.92 (2C), 127.49 (2C), 127.28 (2C) (arom CH), 99.23 (C-1), 83.61 (C-4), 53.04 (–OCH_3), 49.16 (–C$\underline{H}_2$Ph), 47.20 (C-7), 46.94 (C-6), 33.26 (C-5) (1H, d, *J* = 15, C7-$\underline{H}^{a}$).

*8-Benzyl-4-(4-chlorophenyl)-1-hydroxy-6-methoxycarbonyl-4-phenyl-8-aza-2,3-dioxabicyclo[4.3.0]nonan-9-one (***3d***):* colorless crystal, mp 171 ^{o}C; IR (cm^{-1}) 3320 (broad, OH), 1735, 1717 (COO, CON).

*8-Benzyl-1-hydroxy-6-methoxycarbonyl-4-methyl-4-(1-naphthyl)-8-aza-2,3-dioxabicyclo[4.3.0]nonan-9-one (***3e***):* colorless crystal, mp 159 ^{o}C; IR (cm^{-1}) 3268 (broad, OH), 1739, 1715 (COO, CON).

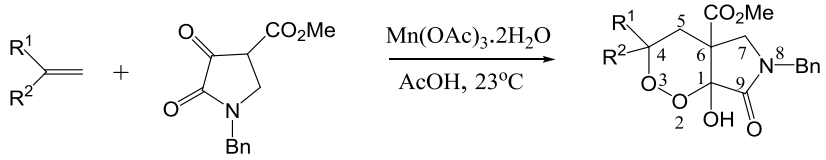
3. RESULTS AND DISCUSSION

3.1. Manganese(III)-catalyzed Reaction of 1,1-Disubstituted ethenes and methyl 1-benzyl-2,3-pyrrolidinedione-4-carboxylate

In an initial experiment, reaction of 1,1-bis(4-methylphenyl)ethene (**1a**) with methyl 1-benzyl-2,3-pyrrolidinedione-4-carboxylate (**2**), and manganese(III) acetate dehydrate with molar ratio of **1**:**2**:$Mn(OAc)_3.2H_2O$ = 1:2:1 in an open flask at 23^{o}C allowed us to obtain product **3a** in 88 % isolated yield (Scheme 1 and Table 1, Entry 1). Trying to carry out similar reactions at the molar ratio of **1**:**2**:$Mn(OAc)_3.2H_2O$ = 1:1.5:1 and 1:2:0.5 resulted in a requirement of longer reaction times and lower product yields (71 and 76 %, respectively). Structure of product **3a** was established by spectroscopic methods. The ^{1}H NMR spectrum of **3a** showed two pairs of doublet (Sheme 2, a). One pair was at 4.53 and 4.26 ppm which we assigned the signals of two hydrogen atoms of benzyl group. The other pair of doublet was due to the absorption of C-7 methylene reasoning that two hydrogen atoms attached to C-7 were diastereotopic. It was worth noting that although C-5 methylene protons were also diastereotopic, but signal splitting was not observed. These protons gave rise to a singlet at 3.02 ppm (scheme 2, a) and was thought to be due to an accidental coincidence.

To demonstrate the efficiency of this synthetic methodology, a range of different 1,1-disubstituted ethenes were prepared and subjected to undergo a similar reaction. The lowest yield was obtained when ethene **1e** was used as starting material (Table

1, Entry 5). Electron-withdrawing groups such as chlorine atom slightly lowered product yield (table 1, Entry 3, 4).

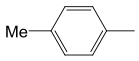
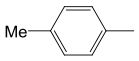
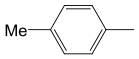
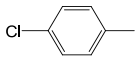
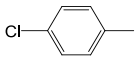
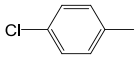
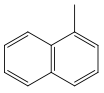


1a-e **2** **3a-e**

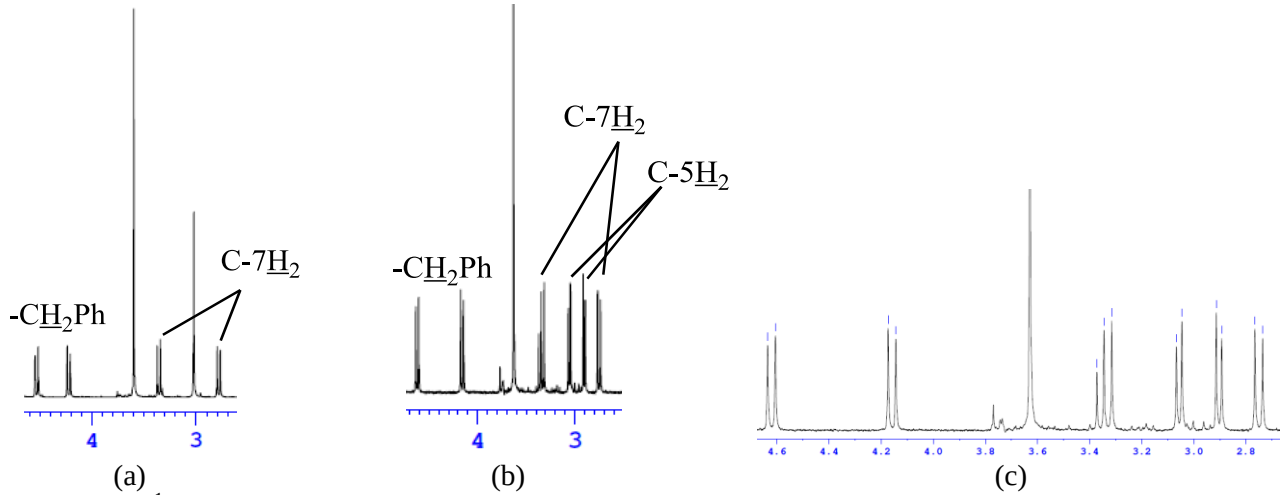
Scheme 1: Reaction of 1,1-diarylethenes **1a-e** with methyl 1-benzyl-2,3-pyrrolidinedione-4-carboxylate **2** in the presence of manganese triacetate dehydrate

It was worth mentioning that, different from the ^{1}H NMR spectrum of **3a** analyzed above, the one of **3c** had three pairs of doublet. Two of which were signals of benzyl and C-7 methylenes. The remained pair of doublet was due to the absorption of two diastereotopic hydrogen atoms of C-5.

Table 1: Reaction of 1,1-disubstituted ethenes **1a-e** with 1-benzyl-2,3-pyrrolidinedione-4-carboxylate in the presence of manganese(III) acetate dihydrate[a]

Entry	Ethene	R^1	R^2	Product (yield %)[b]
1	**1a**			**3a** (88)
2	**1b**			**3b** (80)
3	**1c**			**3c** (72)
4	**1d**			**3d** (74)
5	**1e**			**3e** (43)

[a]The reaction was carried out in glacial acetic acid at 23 °C for 12 hours with the molar ratio of **1**:**2**:Mn(OAc)$_3$.2H$_2$O = 1:2:1. [b]Isolated yield based on the amount of 1,1-disubstituted ethene used.



(a) (b) (c)

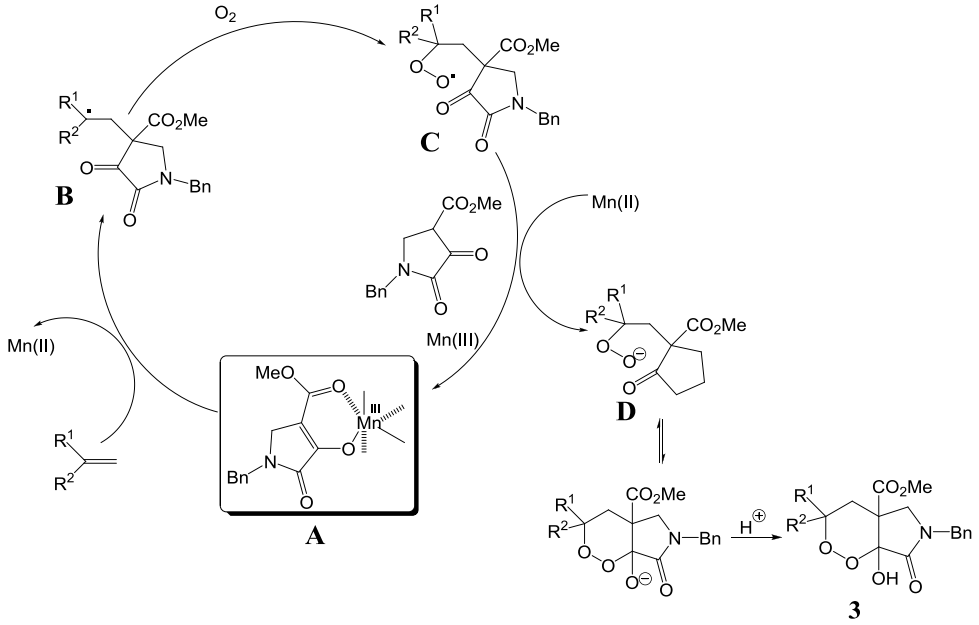
Scheme 2: ^{1}H NMR spectrum of **3a** and **3c** (a) Doublets of –C$\underline{H}_2$Ph and C-7$\underline{H}_2$, (b) Doublets of –C$\underline{H}_2$Ph, C-7$\underline{H}_2$ and C-5$\underline{H}_2$, and (c) Expansion of (b)

3.2. Reaction mechanism

Fristad speculated that enolization of acetic acid ligand was the key step in the formation of radicals from acetic acid derivatives by a manganese(III) acetate-based oxidation system [1a]. In a similar

oxidation system of 2-substituted 1,3-dicarbonyl esters, Snider demonstrated that the key step was also an enolization [1b,c]. For the managanese(II)- and (III)-mediated free radical cyclization of alkenes, *β*-keto esters and molecular oxygen, Yamada and co-workers proposed a mechanism in which manganese(II) reduced peroxyl radicals to give the corresponding peroxyl anions [2]. In our previous publications, we outlined a similar reaction pathway but manganese(II) was the reductant formed along the course [5a,b]. Thus, in this present reaction, the formation of product **3** could be explained through the plausible mechanism depicted in Scheme 3. At the first stage, it is likely that methyl 1-benzyl-2,3-pyrrolidinedione-4-carboxylate forms the corresponding manganese(III) enolate complex **A** with manganese(III) acetate dihydrate *via* a ligand exchange process. Next, it is reasonable that an interaction of complex **A** with the ethene would generate a concerted one-electron transfer from the ethene to Mn(III) center to produce radical **B** at the second stage [10]. An oxygen molecule trapping step of radical **B** would occur to give peroxyl radical **C** which is then reduced with Mn(II) to form anion **D**. A cyclization and subsequent proton capture of **D** to yield product **3** could be the last stage of whole mechanism in which Mn(III) is regenerated after each cycle.

It seemed that bulky 1-naphthyl group of **1e** might cause a steric hindrance according to mechanistic features explained above and therefore gave lowest product yield. In the cases of **1c** and, especially, **1d** lower yields compared to that of **1a** were likely due to the poor stability of the corresponding carbon radical **B**.



Scheme 3: Proposed mechanism for the formation of **3**

4. CONCLUSION

In summary, a number of new 8-aza-2,3-dioxabicyclo[4.3.0]nonan-9-ones possessing different substituents at the 4-position have been synthesized in high yields by using the molecular oxygen trapping reaction of 1,1-disubstituted ethenes with methyl 1-benzyl-2,3-pyrrolidinedione-4-carboxylate in the presence of manganese triacetate dehydrate as a catalyst. Ethene having electron donating substituent significantly improved the product yield.

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REFERENCES

1. (a) W. E. Fristad, J. R. Peterson, A. B. Ernst, G. B. Urbi, G. *Mechanisms for Manganese(III) Oxidations with Alkenes*, Tetrahedron, **42**, 3429-3442 (1986). (b) B. B. Snider, R. Mohan, S. A. Kates. *Manganese(III) Based Oxidative Free Radical Cyclizations 2. Polycyclization Reactions Proceeding Through Tertiary Cations*, Tetrahedron Lett., **28**, 841-844, (1987). (c) B. B. Snider. *Manganese(III)-Based Oxidative Free-Radical Cyclizations*, Chem. Rev., **96**, 339-363 (1996).
2. (a) T. Yamada, Y. Iwahara, N. Hiroshi, K. Kurosawa.

Manganese(II)- and (III)-Mediated Free-Radical Cyclization of Alkenes, β-Keto Esters and Molecular Oxygen, J. Chem. Soc. Perkin Trans., **1**, 609-616 (1993). (b) K. Asahi, N. Nishino. *Manganese(III)-Based Oxidation of 2,4-Piperidinediones in the Presence of Alkenes*, Tetrahedron, **61**, 11107-11124 (2005).

3. (a) W. D. Crow, W. Nicholls, M. Sterns. *Root inhibitors in eucalyptus grandis: Naturally occurring derivatives of the 2,3-dioxabicyclo[4.4.0]decane system*, Tetrahedron Lett., **12**, 1353-1356 (1971). (b) L. Zhang, W.-S. Zhou, X.-X Xu. *A new sesquiterpene peroxide (yingzhaosu C) and sesquiterpenol (yingzhaosu D) from Artabotrys unciatus (L.) Meer.*, J. Chem. Soc., Chem. Commun., 523-524 (1988). (c) D. A. Casteel. *Peroxy natural products*, Nat. Prod. Rep., **16**, 55-73 (1999).
4. V.-H. Nguyen, N. Hiroshi, K. Kurosawa. *Mn(III)-Based facile synthesis of 3-cyano-4,5-dihydrofurans and 4-cyano-1,2-dioxan-3-ols Using alkenes and acylacetonitrile building blocks*, Synthesis, 899-908 (1997).
5. (a) V. -H. Nguyen, N. Hiroshi, K. Kurosawa. *Mn(III)-Induced Molecular Oxygen Trapping Reaction of Alkenes with 2,3-Pyrrolidinedione Derivatives. A Novel Entry to 1-Hydroxy-8-aza-2,3-dioxabicyclo[4.3.0]nonan-9-ones*, Tetrahedron Lett., **38**, 1773-1776, (1997). (b) V.-H. Nguyen, N. Hiroshi, K. Kurosawa. *Mn(III)-Based Reaction of Alkenes with Pyrrolidinedione Derivatives. Formation of Bicyclic Peroxides and the Related Compounds*, Heterocycles, **48**, 465-480 (1998). (c) R. Kumabe, H. Nishino, M. Yasutake, V. -H. Nguyen, K. Kurosawa. *Catalytic oxidation of 4-piperidone-3-carboxylates with manganese(III) acetate in the presence of 1,1-disubstituted alkenes*, Tetrahedron Lett., **42**, 69-72 (2001).
6. E. I. Heiba, R. M. Dessau, W. J. Koehl. *Oxidation by Metal Salts. III. The Reaction of Manganese Acetate with Aromatic Hydrocarbons and the Reactivity of the Carboxymethyl Radical*, J. Am. Chem. Soc., **91**, 138-145 (1969).
7. A. Klages. *Synthesis of Arylated Ethylenebenzenes*, Ber., **35**, 2646-2649 (1902).
8. G. Stork, S. M. McElvain. *Preparation of Ethyl β-benzylaminopropionate and Benzyl-di-(β-carbethoxyethyl)-amine* , J. Am. Chem. Soc., **69**, 971-972 (1947).
9. P. L. Southwick, L. L. Seivard. *The Ring Closure of N-Alkoxalyl-β-anilinopropionic Acids*, J. Am. Chem. Soc., **71**, 2532-2538 (1949).
10. H. Nishino, V.-H. Nguyen, S. Yoshinaga, K. Kurosawa. *Formation of Tetrahydrofuran Derivatives and Acetonylation of Alkenes Using Carbon Radicals Derived from Manganese(III) Oxidation of Diketene*, J. Org. Chem., **61**, 8264-8271, (1996).

Corresponding author: **Nguyen Van Ha**
Department of Chemistry, Dalat University
01 Phu Dong Thien Vuong, Da Lat, Lam Dong, Viet Nam
E-mail: hanv@dlu.edu.vn.