

## Synthesis of 2,7,8-trioxaspiro[4,5]decan-1-ones by manganese(III)-based reaction

Nguyen Van Ha<sup>1\*</sup>, Ta Thi Han Hoan<sup>1</sup>, Nguyen Thi To Uyen<sup>1</sup>, Huynh Thanh Truc<sup>2</sup>, Hiroshi Nishino<sup>3</sup>

<sup>1</sup>Department of Chemistry, Dalat University, 1 Phu Dong Thien Vuong, Dalat, Vietnam

<sup>2</sup>Department of Chemistry, Graduate School of Science and Technology, Kumamoto University, Kurokami, Kumamoto 860-8555, Japan

<sup>3</sup>Department of Chemistry, Faculty of Science, Kumamoto University, Kurokami 2-39-1, Kumamoto 860-8555, Japan

Received 25 July 2017; Accepted for publication 29 December 2017

### Abstract

Some new spiro bicyclic compounds possessing one 1,2-dioxane ring and one  $\gamma$ -lactone ring were successfully synthesized by manganese(III)-based reaction of 1,1-diarylethenes and 2-acetylbutyrolactone under air. The procedure was simple and the product yield was high. The NMR spectrometric features of the products were analyzed and the reaction mechanism is briefly discussed.

**Keywords.** Manganese(III)-based reaction, spiro bicyclic compound, 1,2-dioxane ring,  $\gamma$ -lactone ring.

### 1. INTRODUCTION

Heterocyclic compounds containing the 1,2-dioxane moiety are found in many natural products and some of them exhibit significant biological activities [1]. On the other hand, spiro lactones are a versatile class of lactones due to their pharmaceutical properties and are still receiving considerable attention today [2]. Hence, it seems likely that the synthesis of spiro compounds having the above mentioned two structural features could be a topic of interest. 1,2-Dioxanes were successfully synthesized by a [2+2+2] cycloaddition of olefin, 1,3-diketone and molecular oxygen. This cycloaddition was made possible by using an electrochemical method [3] or a manganese(III)-based reaction [4]. However, reports on the formation of spiro bicycles having both  $\gamma$ -lactone and 1,2-dioxane rings are extremely rare. As far as we can see, only one compound of this kind was afforded by using a mixture of manganese(II) and (III)-mediated reaction [5]. Recently, we described a simple route to 2-oxa-7-azaspiro[4.4]nonane-8,9-diones using Mn(III)-based oxidation of 4-acylpyrrolidine-2,3-diones [6]. As part of a study aimed at expanding the synthetic utility of manganese(III) system to synthesize bicyclic spiro compounds, we examined the [2+2+2] cycloaddition of 1,1-diarylethene, 2-acetylbutyrolactone, and molecular oxygen and

found that this reaction might be a practical route to spirobicycles possessing both  $\gamma$ -lactone and 1,2-dioxane rings. Herein, we wish to show our work.

### 2. EXPERIMENTAL

#### 2.1. Measurements

All of the <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on a JNM-AL 300 FT NMR spectrometer at 300 MHz for <sup>1</sup>H and 75 MHz for <sup>13</sup>C or on a Bruker Avance 500 FT NMR spectrometer at 500 MHz for <sup>1</sup>H and 125 MHz for <sup>13</sup>C, with tetramethylsilane as the internal standard. The chemical shifts are shown in  $\delta$  values (ppm) and coupling constants in Hz. The IR spectra were measured on a Thermo Scientific Nicolet iS5 FT-IR spectrometer and the IR spectral data are expressed in cm<sup>-1</sup>. The high-resolution mass spectra were recorded using a JEOL JMS-700 MStation.

#### 2.2. Materials

Manganese(III) acetate dihydrate, Mn(OAc)<sub>3</sub>·2H<sub>2</sub>O, was prepared according to the literature method [7]. 1,1-Diarylethenes **1a-d** were prepared by dehydration of the corresponding alcohols, which were synthesized from substituted acetophenones and arylmagnesium bromides [8]. Manganese(II)

acetate tetrahydrate and glacial acetic acid were purchased from Wako Pure Chemical Ind., Ltd., 2-acetylbutyrolactone from Sigma-Aldrich Co. LLC. and was used as received.

### 2.3. Reaction procedure

A general procedure is as follows. 1,1-Diarylethene (0.25 mmol) was weighed into a 30 mL flask equipped with a magnetic stirrer. Glacial acetic acid (10 mL), 2-acetylbutyrolactone (0.75 mmol), and manganese triacetate dihydrate (0.25 mmol) were added. The mixture was stirred at 23 °C for 10 hours under air. Then, the solvent was removed *in vacuo*, and the residue was triturated with water. The aqueous mixture was extracted three times with chloroform (10 mL for the first and 5 mL each for the second and the last). The combined extracts were dried over anhydrous sodium sulfate, filtered and concentrated to dryness. The products were separated on silica gel TLC (Wakogel B-10 or Merck Kieselgel 60 F<sub>254</sub>) with dichloromethane:methanol (99:1 in v/v) as the developing solvent.

### 2.4. Product data

*Stereoisomeric mixture of 6-hydroxy-6-methyl-9,9-diphenyl-2,7,8-trioxaspiro[4.5]decan-1-one (3a)*: colorless microcrystals (from chloroform), mp 127.5-129.5 °C; IR (KBr) 3426.5 (–OH), 1738.7 (–COO–); <sup>1</sup>H NMR (CDCl<sub>3</sub>, δ) 7.56-7.23 (10H, m, arom H), 4.24-4.02 (2H, m, CH<sub>2</sub>, C3), 3.41, 3.26, 2.76, 2.62 (2H, d, *J* = 14, CH<sub>2</sub>, C10), 1.81-1.49 (2H, m, CH<sub>2</sub>, C5), 1.44, 1.38 (3H, s, CH<sub>3</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>, δ) 177.90, 177.69 (–COO–), 142.11, 141.52 (arom C), 128.51, 128.49 (2C), 128.31, 128.24, 127.30, 127.15, 126.73, 126.31, 126.05 (arom CH), 102.10, 99.40 (C6), 84.80, 83.96 (C9), 67.88, 66.11 (C3), 48.96, 47.28 (C5), 41.29, 37.69 (C10), 35.20, 31.61 (C4), 22.66, 21.78 (CH<sub>3</sub>); FAB HRMS (acetone/NBA/NaI): calcd for C<sub>20</sub>H<sub>20</sub>O<sub>5</sub>Na 363.1208 (M+Na); found 363.1209.

*Stereoisomeric mixture of 6-hydroxy-9,9-bis(4-methylphenyl)-6-methyl-2,7,8-trioxaspiro[4.5]decan-1-one (3b)*: colorless microcrystals (from chloroform), mp 139.5-141.5 °C; IR (KBr) 3418.0 (–OH), 1751.0 (–COO–); <sup>1</sup>H NMR (CDCl<sub>3</sub>, δ) 7.41-7.07 (8H, m, arom H), 4.24-4.02 (2H, m, CH<sub>2</sub>, C3), 3.38, 3.24, 2.71, 2.56 (2H, d, *J* = 14, CH<sub>2</sub>, C10), 2.31, 2.27 (CH<sub>3</sub>), 1.82-1.65 (2H, m, CH<sub>2</sub>, C5), 1.45, 1.37 (3H, s, CH<sub>3</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>, δ) 178.01, 177.77 (–COO–), 138.66, 138.36, 136.89, 139.69 (arom C), 129.13 (2C), 128.89 (2C), 126.63 (2C), 126.33 (2C) (arom CH),

105.57, 102.06 (C6), 84.72, 83.89 (C9), 67.88, 66.11 (C3), 48.97, 47.33 (C5), 41.23, 37.64 (C10), 35.25, 31.70 (C4), 21.75, 21.00 (CH<sub>3</sub>); FAB HRMS (acetone/NBA/NaI): calcd for C<sub>22</sub>H<sub>24</sub>O<sub>5</sub>Na 391.1521 (M+Na); found 391.1527.

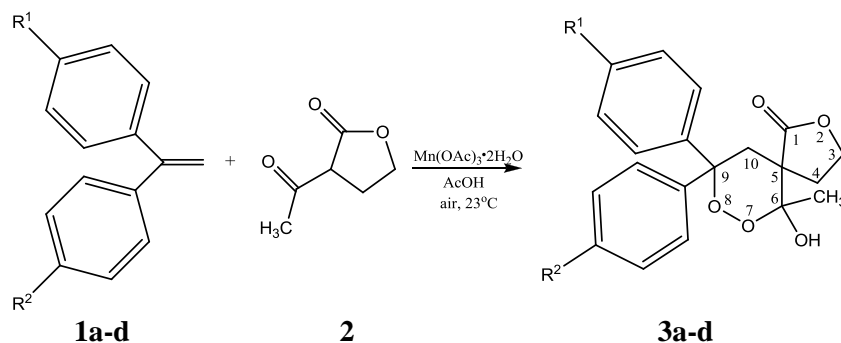
*Stereoisomeric mixture of 9,9-bis(4-chlorophenyl)-6-hydroxy-6-methyl-2,7,8-trioxaspiro[4.5]decan-1-one (3c)*: colorless microcrystals (from chloroform), mp 143.5-145.0 °C; IR (KBr) 3430.5 (–OH), 1751.0 (–COO–); <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, δ) 7.60-7.32 (8H, m, arom H), 4.10-4.02 (2H, m, CH<sub>2</sub>, C3), 3.16-2.79 (2H, m, CH<sub>2</sub>, C10), 1.80-1.57 (2H, m, CH<sub>2</sub>, C5), 1.24 (3H, s, CH<sub>3</sub>); <sup>13</sup>C NMR (DMSO-d<sub>6</sub>, δ) 177.37, 175.60 (–COO–), 142.18, 140.91, 132.63, 1231.79 (arom C), 128.5 (2C), 128.32, 128.06 (2C), 127.67, 127.36 (2C) (arom CH), 101.48, 99.28 (C6), 83.14, 82.69 (C9), 67.22, 65.34 (C3), 48.52, 46.72 (C5), 36.35 (2C, C10), 31.5, 30.76 (C4), 21.36, 21.35 (CH<sub>3</sub>); FAB HRMS (acetone/NBA/NaI): calcd for C<sub>20</sub>H<sub>18</sub>O<sub>5</sub>Cl<sub>2</sub>Na 431.0429 (M+Na); found 431.0438.

*Stereoisomeric mixture of 9,9-bis(4-fluorophenyl)-6-hydroxy-6-methyl-2,7,8-trioxaspiro[4.5]decan-1-one (3d)*: colorless microcrystals (from chloroform), mp 141.5-143.5 °C; IR (KBr) 3434.6 (–OH), 1746.9 (–COO–); <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, δ) 7.62-7.10 (10H, m, arom H), 4.09-4.03 (2H, m, CH<sub>2</sub>, C3), 3.17, 3.14, 2.86, 2.80 (2H, d, *J* = 14, CH<sub>2</sub>, C10), 1.73-1.60 (2H, m, CH<sub>2</sub>, C5), 1.25 (3H, s, CH<sub>3</sub>); <sup>13</sup>C NMR (DMSO-d<sub>6</sub>, δ) 177.49, 175.71 (–COO–), 162.33, 162.02, 160.38, 160.08, 139.81, 139.63, 139.51, 139.40 (arom C), 128.15, 128.08, 115.32, 115.15, 114.86, 114.69 (arom CH), 101.45, 99.19 (C6), 89.16, 82.78 (C9), 67.26, 65.35 (C3), 48.56, 46.73 (C5), 36.98 (2C, C10), 31.46, 30.69 (C4), 21.33 (2C, CH<sub>3</sub>); FAB HRMS (acetone/NBA/NaI): calcd for C<sub>20</sub>H<sub>18</sub>O<sub>5</sub>F<sub>2</sub>Na 399.1020 (M+Na); found 399.1023.

## 3. RESULTS AND DISCUSSION

### 3.1. Manganese(III)-based reaction of 1,1-diarylethenes 1a-d with 2-acetylbutyrolactone under air

In an initial experiment, the manganese(III)-based molecular oxygentrapping reaction was examined by stirring a mixture of 1,1-diphenylethene **1a** (0.25 mmol), 2-acetylbutyrolactone **2** (0.5 mmol), manganese(III) acetate dihydrate (0.125 mmol), and glacial acetic acid (10 mL) at 23 °C for 16 hours under air. Separation of the product mixture by thin layer chromatography provided the desired 6-hydroxy-methyl-9,9-diphenyl-2,7,8-



(a:  $R^1 = R^2 = C_6H_5$ , b:  $R^1 = R^2 = CH_3C_6H_4$ , c:  $R^1 = R^2 = ClC_6H_4$ , d:  $R^1 = R^2 = FC_6H_4$ )

*Scheme 1:* Manganese(III)-based molecular oxygen trapping reaction of 1,1-diarylethenes with 2-acetylbutyrolactone

trioxaspiro[4.5]decan-1-one **3a** in 65% isolated yield (Scheme 1, Ar =  $C_6H_5$  and table 1, entry 1). In an attempt to improve the product yield, several reactions were performed in various molar ratios of which 1:3:1 ratio of 1,1-diphenylethene:2-acetylbutyrolactone:manganese(III) acetate dihydrate gave the highest yield (table 1, entry 4). Decreasing the amount of manganese(III) acetate dihydrate prolonged the reaction time and lowered the product yield. On the other hand, increasing the amount of 2-acetylbutyrolactone afforded a comparable yield, however it made the product isolation more difficult and consumed more time.

To our surprise,  $^{13}C$  NMR spectrum of this product consisted of almost pairs of signals. This was saying, reasonably enough, the NMR sample contained two close compounds. Comparing  $^{13}C$  NMR and  $^{13}C$  DEPT data of this product with that

of the compound reported in the literature [5] led to a conclusion that our product was supposedly obtained as a mixture of two isomers of 6-hydroxy-6-methyl-9,9-diphenyl-2,7,8-trioxaspiro[4.5]decan-1-one.

Basing on MM2 calculation, Yamada and co-workers reported that among possible four stereostructures of 6-hydroxy-6-methyl-9,9-diphenyl-2,7,8-trioxaspiro[4.5]decan-1-one, (*E*)-[*e* (OH), *e*] isomer possesses the lowest energy [5]. We reason that although (*E*)-[*a* (OH), *a*] isomer has a higher energy than (*E*)-[*e* (OH), *e*] isomer, the energetic difference is not much (25.9 kcal mol<sup>-1</sup> vs. 24.2 kcal mol<sup>-1</sup>, respectively). Thus, in our reaction, these two compounds could be formed in a certain proportion. Unfortunately, at present time we are not able to calculate the percentage of each isomer in the product mixture.

*Table 1:* Manganese(III)-based molecular oxygen trapping reaction of 1,1-diphenylethene (**1a**) with 2-acetylbutyrolactone<sup>a</sup>

Entry	Ethene	Molar ratio <sup>b</sup>	Time (hour)	Yield of <b>3a</b> (%) <sup>c</sup>
1	<b>1a</b>	1:2:0.5	16	64
2	<b>1a</b>	1:2:1	12	76
3	<b>1a</b>	1:3:0.5	15	70
4	<b>1a</b>	1:3:1	10	83

<sup>a</sup>The reactions were carried out in glacial acetic acid under air.

<sup>b</sup>1,1-Diphenylethene:2-acetobutyrolactone:manganese(III) acetate dihydrate.

<sup>c</sup>Yields based on 1,1,diphenylethene used.

We next turned our attention to the synthesis of some new 2,7,8-trioxaspiro[4.5]decan-1-ones. This was done by applying the above reaction to 1,1-diarylethenes different from 1,1-diphenylethene.

The results of our experiments are shown in table 2. Apparently, for reasons that are currently unknown, the results revealed that moderate electron withdrawing Cl group increased product yield,

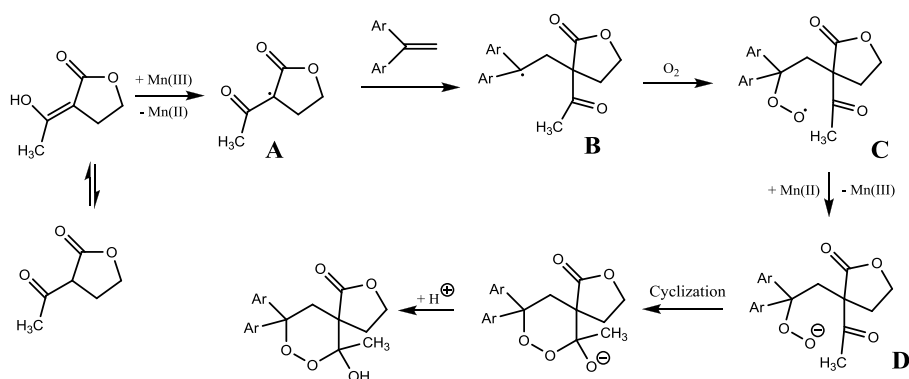
though not much, while strong electron withdrawing F group and electron releasing CH<sub>3</sub> group lowered the yields.

Table 2: Manganese(III)-based molecular oxygen trapping reaction of 1,1-diarylethenes (**1c-d**) with 2-acetylbutyrolactone<sup>a</sup>

Entry	Ethene	Product	Yield (%) <sup>b</sup>
1	<b>1b</b>	<b>3b</b>	76
2	<b>1c</b>	<b>3c</b>	85
3	<b>1d</b>	<b>3d</b>	70

<sup>a</sup>The reactions were carried out at the molar ratio of 1,1-diarylethene:2-acetobutyrolactone:manganese(III) acetate dihydrate = 1:3:1 in glacial acetic acid at 23 °C under air for 10 hours.

<sup>b</sup>The yield based on 1,1-diarylethene used.



Scheme 2: Plausible reaction mechanism

#### 4. CONCLUSION

We have applied the manganese(III)-based reaction to a [2+2+2] cycloaddition of 1,1-diarylethenes, 2-acetylbutyrolactone, and molecular oxygen. This application allowed us to synthesize four spiro bicyclic products of which three have not yet been reported. The involving of both  $\gamma$ -lactone and 1,2-dioxane rings to spiro skeleton is attractive. We believe that this approach could be employed in preparation of other new 2,7,8-trioxaspiro[4.5]decan-1-ones as well.

#### REFERENCES

- (a) 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., **8**, 523-524 (1988). (b) D. A. Casteel. *Peroxy natural products*, Nat. Prod. Rep., **16(1)**, 55-73 (1999).
- Forexample: (a) S. E. Kiruthika, R. Amritha, P. T. Peramal. *An Efficient Strategy for Functionalized Spirolactones and Dispirodihydrofuranyl Oxindoles Using Amines and Activated Alkynes*, Tetrahedron Lett., **53(26)**, 3268-3273 (2012). (b) J. R. Syu, C. H. Lin, C. W. Kuo, D. Y. Yan. *Synthesis of Benzofuran-containing Spirolactones from Diarylcyclopropenones*, Tetrahedron Lett., **55(6)**, 1207-1211 (2014). (c) Niharika, P., Satyanarayana, G., *One-pot C=C/C=O bond formation. Synthesis of spirocyclic Lactones*, RSC. Adv., **6**, 837-843 (2016).
- (a) J. Yoshida, K. Sakaguchi, S. Isoe, K. Hirotsu. *Electro-initiated [2+2+2] cycloaddition of molecular oxygen, olefin, and 1,3-diketone*, Tetrahedron Lett., **28(6)**, 667-670 (1987). (b) J. Yoshida, S. Nakatani, K. Sakaguchi, S. Isoe. *Formal [2+2+2] cycloaddition of molecular oxygen, 1,3-diketone, and olefin. Synthesis and reactions of cyclic peroxides*, J. Org.

- Chem., **54(14)**, 3383-3389 (1989).
4. S. Tategami, T. Yamada, H. Nishino, J. D. Korp, K. Kurosawa. *Formation of 1,2-dioxacyclohexanes by the reaction of alkenes with tris(2,4-pentanedionato)manganese(III) or with  $\beta$ -keto carbonyl compounds in the presence manganese(III) acetate*, Tetrahedron Lett., **31(44)**, 6371-6374 (1990).
  5. T. Yamada, Y. Iwahara, H. Nishino, K. Kurosawa. *Manganese(II)- and (III)-mediated Free-radical Cyclization of Alkenes,  $\beta$ -Keto Esters and Molecular Oxygen*, J. Chem. Soc. Perkin Trans., **1(5)**, 609-616 (1993).
  6. T.-T. Huynh, V.-H. Nguyen, H. Nishino. *One-pot synthesis of 2-oxa-7-azaspiro[4.4]nonane-8,9-diones using Mn(III)-based oxidation of 4-acylpyrrolidine-2,3-diones*, Tetrahedron Lett., **58(37)**, 3619-3622 (2017).
  7. 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).
  8. A. Klages. *Synthesis of Arylated Ethylenebenzenes*, Ber., **35**, 2646-2649 (1902).
  9. (a) W. E. Fristad, J. R. Peterson, A. B. Ernst, G. B. Urbi G. *Mechanisms for Manganese(III) Oxidations with Alkenes*, Tetrahedron, **42(13)**, 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(1)**, 841-844 (1987).
  10. H. Nishino, V.-H. Nguyen, S. Yoshinaga, K. Kurosawa. *Formation of Tetrahydrofuran Derivatives and Acetylation of Alkenes Using Carbon Radicals Derived from Manganese(III) Oxidation of Diketene*, J. Org. Chem., **61(23)**, 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.