Available online at www.sciencedirect.com

ScienceDirect

Chinese Chemical Letters 21 (2010) 686–689

CHINESE CHEMICAL LETTERS

www.elsevier.com/locate/cclet

An efficient synthesis of 2,2′-arylmethylene bis (3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) and 1,8-dioxooctahydroxanthenes using ZnO and ZnO–acetyl chloride

Malek Taher Maghsoodlou *, Sayyed Mostafa Habibi-Khorassani, Zahra Shahkarami, Nariman Maleki, Mohsen Rostamizadeh

Department of Chemistry, The University of Sistan and Baluchestan, P.O. Box 98135-674, Zahedan, Iran

Received 21 October 2009

Abstract

2,2′-Arylmethylene bis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) **4l-s** produced from reaction between dimedone with various aldehydes in acetonitrile using ZnO as a catalyst; whereas in the presence of ZnO–acetyl chloride catalysts the reaction is limited to give only 1,8-dioxo-octahydroxanthenes **3a-k** in very good yields.

Keywords: ZnO; ZnO–acetyl chloride; Dimedone; Aldehyde; 1,8-Dioxooctahydroxanthene; 2,2′-Arylmethylene bis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one)

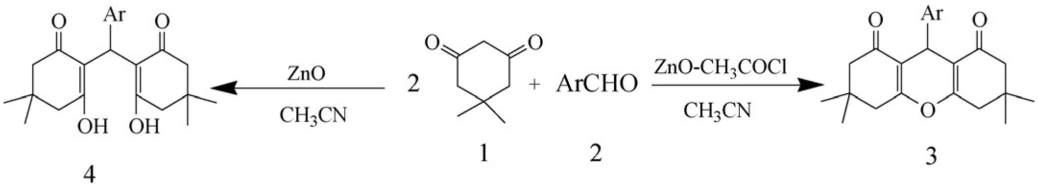
Xanthenes are an important class of organic compounds that find use as dyes, fluorescent material for visualization of biomolecules and in laser technologies due to their useful spectroscopic properties [1,2]. Xanthenes have also received significant attention from many pharmaceutical and organic chemists essentially because of the broad spectrum of their biological and pharmaceutical properties such as antiviral [3], antibacterial [4]. There are several reports in the literature for the synthesis of xanthene and 1,8-dioxooctahydroxanthene derivatives [5–10]. Each of these methods have their own advantages but also suffer from one or more disadvantages such as prolonged reaction time, tedious work-up processes, low yield, lack of easy availability, preparation of starting materials and hazardous reaction conditions. Zinc oxide is an inexpensive, moisture stable, reusable, commercially available and environmentally benign catalyst used in Beckmann rearrangements [11], Friedel–Crafts acylation [12], and synthesis of cyclic ureas [13]. In continuation of our work [14,15], we examined ZnO and ZnO–acetyl chloride for synthesis of 2,2′-arylmethylenebis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) and 1,8-dioxooctahydroxanthenes. Initially we examined ZnO as heterogeneous catalyst in the condensation of 5,5-dimethyl-1,3-cyclohexanedione **1** with benzaldehyde **2a** refluxing in acetonitrile. Surprisingly, contrary to our expectation, only intermediate 2,2′-phenylmethylenebis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) **4l** is obtained in 92% yield. Cyclized product **3a** was not obtained. Prolonging the reaction time and increase in catalyst amount ZnO (80 mol%) did not yield the

---

* Corresponding author.

E-mail address: mt_maghsoodlou@yahoo.com (M.T. Maghsoodlou).

1001-8417/$ – see front matter © 2010 Malek Taher Maghsoodlou. Published by Elsevier B.V. on behalf of Chinese Chemical Society. All rights reserved.
doi:10.1016/j.cclet.2010.02.005



Scheme 1. Synthesis of 9-aryl-1,8-dioxooctahydroxanthene derivatives **3** and 2,2′-arylmethylene bis(3-hydroxy-2-cyclohexene-1-one) derivatives **4** in acetonitrile.

Table 1
Synthesis of 9-aryl-1,8-dioxooctahydroxanthene derivatives **3** and 2,2′-arylmethylene bis(3-hydroxy-2-cyclohexene-1-one) derivatives **4** in acetonitrile.

Entry	Ar	Product	Time (h)	Yield (%)	M.P. (°C) [16–21]
1	C_6H_5	3a	5	86	203–204
2	4-(NO_2)–C_6H_5	3b	2	96	224–226
3	3-(NO_2)–C_6H_5	3c	2.5	94	171–173
4	3-(Cl)–C_6H_5	3d	4	94	180–182
5	2-(Cl)–C_6H_5	3e	4.5	92	226–228
6	2-(Cl), 6-(F)–C_6H_5	3f	3	92	117–119
7	3-(OMe), 4(OH)–C_6H_5	3g	6	88	224–225
8	4-(NMe_2)–C_6H_5	3h	6	82	224–226
9	4-(Me)–C_6H_5	3i	5	96	216–218
10	3,4-(OCH_3)$_2$–C_6H_5	3j	6	89	184–186
11	4-(OH)–C_6H_5	3k	5	95	245–246
12	C_6H_5	4l	12	92	187–189
13	4-(NO_2)–C_6H_5	4m	6	92	187–189
14	4-(Me)–C_6H_5	4n	15	89	131–133
15	4-(Cl)–C_6H_5	4o	8	90	141–143
16	4-(NMe_2)–C_6H_5	4p	10	86	182–184
17	4-(OH)–C_6H_5	4q	10	85	202–204
18	3-(Cl)–C_6H_5	4r	8	90	179–181
19	2,4-(Cl_2)–C_6H_5	4s	8	92	190–192

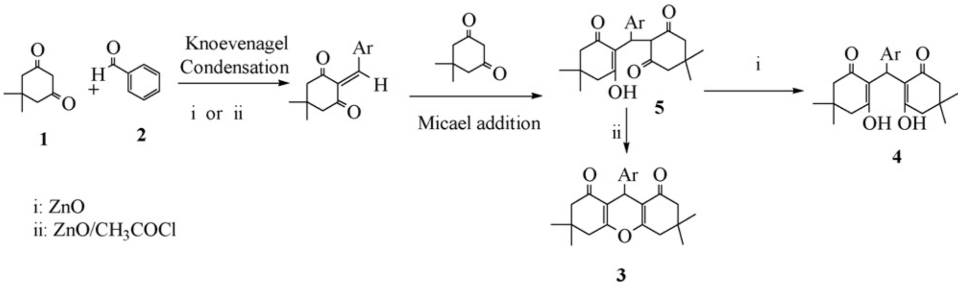
cyclized product **3a**. We have chosen ZnO–acetyl chloride for further study. When ZnO–acetyl chloride is used, the condensation of dimedone **1** with benzaldehyde **2a** proceeds smoothly to give 1,8-dioxooctahydroxanthene **3a** in excellent yield in acetonitrile as well as under reflux (Scheme 1). The amount of zinc oxide was optimized in the reaction and the optimum amount of ZnO was found to be 30 mol%.

It is also noticed that the condensation using ZnO–acetyl chloride proceeds rapidly and is superior to the reported procedures with respect to reaction time, temperature and yield (Table 1).

The spectral data and physical properties of 1,8-dioxooctahydroxanthene and 2,2′-phenylmethylenebis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) derivatives were in agreement with those of literatures reported [16–21]. It is evident that the catalyst plays crucial role in limiting the reaction to the desired level, to yield products **3** or **4**. The hypothesis supported the fact that reaction proceeds via one-pot Knoevenagel condensation, Michael addition and cyclodehydration (Scheme 2). Furthermore, the reaction was also performed in the presence of $ZnCl_2$ as catalyst, as a result, the product was same but the 1,8-dioxooctahydroxant generated in longer time with low yield. Nevertheless, there is no clear evidence for just proceeding the reaction with formation of $ZnCl_2$ in reaction media.

Under the reaction conditions several aromatic aldehydes containing electron donating as well as electron withdrawing groups with diverse substitution pattern were effectively cyclized to give 1,8-dioxooctahydro-xanthenes.

In conclusion, we have represent ZnO–acetyl chloride as a highly and efficient catalyst in one-pot Knoevenagel condensation, Michael addition for cyclodehydration synthesis of 9-aryl-1,8-dioxooctahydro-xanthene derivatives (**3a-k**) by the condensation of an aromatic aldehydes and dimedone under reflux conditions in excellent yields. When ZnO catalyst used in our research works, the reaction is limited to give only 2,2′-arylmethylenebis(3-hydroxy-5,5-dimethyl- 2-cyclohexene-1-one) derivatives (**4l-s**) in very good yields.



Scheme 2. Mechanism for the synthesis of compounds **3** and **4** in acetonitrile.

1. Experimental

*1.1. General procedure for the synthesis of octahydroxanthenes **3a-k***

The aldehyde (**2**) (1 mmol), 5,5-dimethyl-1,3-cyclohexanedione (**1**) (2 mmol), ZnO (30 mol%) and acetyl chloride (2 mmol) were mixed in 20 mL acetonitrile at reflux condition (80 °C). The reaction mixture was refluxed for the time indicated in Table 1. Completion of the reaction was monitored by TLC. After completion of the reaction, the mixture was cooled and poured into 50 mL of ice water. The solid residue was separated and dissolved in dichloromethane. The solution was filtered and zinc oxide was isolated and could be reused. The organic phase was evaporated and the reaction mixture was recrystallized in ethanol to generate pure crystalline product. The obtained solid product washed with cold water (20 mL) and dried for generation of the pure crystalline product.

*1.2. General procedure for the synthesis of 2,2′-arylmethylene bis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) **4l-s***

The aldehyde (**2**) (1 mmol), 5,5-dimethyl-1,3-cyclohexanedione (**1**) (2 mmol), ZnO (30 mol%) were mixed in 20 mL acetonitrile at reflux condition (80 °C). The reaction mixture was refluxed for the time indicated in Table 1. Completion of the reaction was monitored by TLC. After completion of the reaction, the mixture was cooled and poured into 50 mL of ice water. The solid residue was separated and dissolved in dichloromethane. The solution was filtered and zinc oxide was isolated and could be reused. The organic phase was evaporated and the reaction mixture was recrystallized in ethanol to obtain pure crystalline product. The obtained solid product washed with cold water (20 mL) and dried for generation of the pure crystalline product.

Selected spectral data:

Compound **3a**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.00 (s, 6H, CMe_2); 1.11 (s, 6H, CMe_2); 2.14–2.27 (q, 4H, $J = 16.3$ Hz, 2× CH_2); 2.47 (s, 4H, 2× CH_2); 4.76 (s, 1H, CH); 7.01–7.32 (m, 5H, Ar). Anal. Calcd. for $C_{23}H_{26}O_3$: C, 78.83; H, 7.48. Found: C, 78.80; H, 7.52.

Compound **3h**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.01 (s, 6H, CMe_2); 1.10 (s, 6H, CMe_2); 2.14–2.27 (q, 4H, $J = 16.2$ Hz, 2× CH_2); 2.46 (s, 4H, 2× CH_2); 2.88 (s, 6H, NMe_2); 4.67 (s, 1H, CH); 6.63–7.14 (m, 4H, Ar). Anal. Calcd. for $C_{25}H_{31}NO_3$: C, 76.30; H, 7.94; N, 3.56. Found: C, 76.35; H, 7.90; N, 3.50.

Compound **4m**: ^{1}H NMR (80 MHz, $CDCl_3$): δ 1.07 (s, 12H, 4× CH_3); 2.34 (s, 8H, 4× CH_2); 5.47 (s, 1H, CH); 7.11–9.11 (m, 4H, Ar); 11.69 (brs, 2H, 2× OH). Anal. Calcd. for $C_{23}H_{27}NO_6$: C, 66.81; H, 6.58; N, 3.39. Found: C, 66.77; H, 6.60; N, 3.36.

Compound **4n**: ^{1}H NMR (80 MHz, $CDCl_3$): δ 1.09 (s, 12H, 4× CH_3); 2.23 (s, 4H, 2× CH_2); 2.32 (s, 4H, 2× CH_2); 5.44 (s, 1H, CH); 6.64–7.19 (m, 4H, Ar); 11.69 (brs, 2H, 2× OH). Anal. Calcd. for $C_{24}H_{30}O_4$: C, 75.36; H, 7.91. Found: C, 75.40; H, 7.88.

Acknowledgment

We gratefully acknowledge financial support from the Research Council of University of Sistan and Baluchestan, Iran.

References

[1] S.M. Menchen, S.C. Benson, J.Y.L. Lam, et al., US Patent, US 6,583,168 (2003).
[2] A. Banerjee, A.K. Mukherjee, Stain Technol. 56 (1981) 83.
[3] R.W. Lambert, J.A. Martin, J.H. Merrett, et al., PCT Int. Appl. WO 9706178, 1997, Chem. Abstr. 126 (1997) 212377y.
[4] T. Hideo, Jpn. Tokkyo Koho JP. 1981, 56005480, Chem. Abstr. 95 (1981) 80922b.
[5] G.C. Li, J. Chem. Res. (2008) 484.
[6] X.S. Fan, Y.Z. Li, X.Y. Zhang, et al. Chin. Chem. Lett. 16 (2005) 897.
[7] M.A. Bigdeli, F. Nemati, G.H. Mahdavinia, et al. Chin. Chem. Lett. 20 (2009) 1275.
[8] T.S. Jin, J.S. Zang, A.Q. Wang, et al. Synth. Commun. 35 (2005) 2339.
[9] G.H. Mahdavinia, M.A. Bigdeli, Y. SaeidiHayeniaz, Chin. Chem. Lett. 20 (2009) 539.
[10] P. Srihari, S.S. Mandal, J.S.S. Reddy, et al. Chin. Chem. Lett. 19 (2008) 771.
[11] H. Sharghi, M. Hosseini, Synthesis (2002) 1057.
[12] M. Hosseini Sarvari, H. Sharghi, J. Org. Chem. 69 (2004) 6953.
[13] Y.J. Kim, R.S. Varma, Tetrahedron Lett. 45 (2004) 7205.
[14] M.T. Maghsoodlou, A. Hassankhani, H.R. Shaterian, et al. Tetrahedron Lett. 48 (2007) 1729.
[15] A. Hassankhani, M.T. Maghsoodlou, S.M. Habibi-Khorassani, et al. Arkivoc ii (2008) 134.
[16] X. Fan, X. Hu, X. Zhang, et al. Can. J. Chem. 83 (2005) 16.
[17] T.S. Jin, J.S. Zhang, J.C. Xiao, et al. Synth. Lett. 5 (2004) 866.
[18] E.C. Horning, M.G. Horning, J. Org. Chem. 11 (1946) 95.
[19] P. Shanmugasundaram, K.J. Prabahar, V.T. Ramakrishnan, J. Heterocycl. Chem. 30 (1993) 1003.
[20] X.D. Chen, F.P. Xu, J. Shanghai Univ. (Nat. Sci.) 6 (2000) 375.
[21] S. Kantevari, R. Bantu, L. Nagarapu, J. Mol. Catal. A 269 (2007) 53.