HETEROCYCLES, Vol. 75, No. 12, 2008, pp. 3077 - 3083. © The Japan Institute of Heterocyclic Chemistry
Received, 4th June, 2008, Accepted, 15th August, 2008, Published online, 18th August, 2008. COM-08-11459

EFFICIENT SYNTHESIS OF 1,8-DIOXO-OCTAHYDROXANTHENES USING $HClO_4/SiO_2$ AS CATALYST

Gholam Hossein Mahdavinia,[a] Mohammad A. Bigdeli,[b]* Yaser Saeidi Hayeniaz,[b] and Firouzeh Nemati[b]

[a]Department of Chemistry, Islamic Azad University-Marvdasht Branch, Marvdasht, Iran. Fax: +98 728 3338686; E-mail: hmahdavinia@gmail.com.
[b]Faculty of Chemistry, Tarbiat Moalem University, 49 Mofateh St., Tehran, Iran.
Fax: +98 21 88820993; E-mail: mabig397@yahoo.com

Abstract – Silica supported perchloric acid ($HClO_4/SiO_2$) is found to be a heterogeneous recyclable catalyst for rapid and efficient synthesis of 1,8-dioxo-octahydroxanthenes with good to excellent yields in solvent free conditions. The catalyst is easily prepared, stable, reusable and efficiently used under reaction condition.

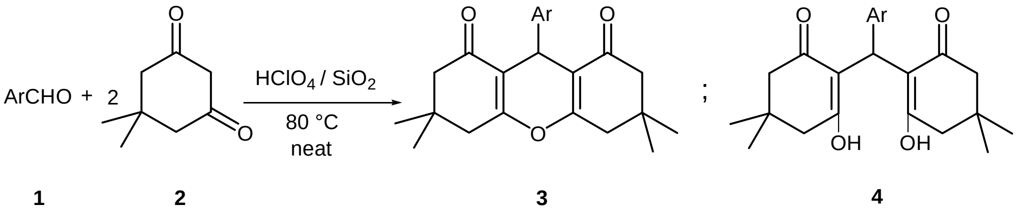
INTRODUCTION

Xanthenes and benzoxanthenes are important classes of compounds that have found use as dyes, fluorescent materials for visualization of bio-molecules and laser technologies due to their useful spectroscopic properties[1-3] Xanthene-based compounds have also been investigated for agricultural bacterial activity,[4] photodynamic therapy,[5] anti-inflammatory effect[6] and antiviral activity.[7] Numerous references are available on the synthesis of xanthenes including palladium catalyzed cyclization of polycyclic aryltriflate esters,[8] intramolecular trapping of benzynes by phenols[9,10] and reaction of aryloxymagnesium halides with triethylorthoformate.[11,12] These methodologies, however, have disadvantages such as low yields, lack of availability or difficulty in preparation of starting materials, prolonged reaction time (16 h to 5 days), and use of toxic organic solvents and excess employment of reagents or catalysts. *p*-Dodecylbenzenesulfonic acid (DBSA) in aqueous media,[13,14] *p*-toluenesulfonic acid (*p*–TsOH) in organic solvents,[15] heterogeneous catalysts ($NaHSO_4$-SiO_2 and silica chloride),[16] $InCl_3\cdot4H_2O$ in ionic liquid,[17] Amberlyst-15,[18] polyaniline-*p*-toluenesulfonate salt[19] and PPA-SiO_2[20] are also reported. Many of these methods, however, have similar shortcoming to the previously mentioned methods. Hence it is important to be on the lack out for more convenient methods.

The leading contenders for environmentally acceptable processes are supported reagents. Use of silica-supported reagents in one-pot multi-component construction of heterocycles has received considerable attention in organic synthesis.[21] Perchloric acid adsorbed on silica gel ($HClO_4/SiO_2$)[22] has immerged as an extremely useful catalyst in various organic transformations.[23-37]

In view of its inherent properties such as environmental compatibility, greater selectivity, operational simplicity, moisture-insensitively, noncorrosive nature and ease of isolation, we set out to find out more about the behavior of $HClO_4$ supported on silica gel (230-400 mesh) in the synthesis of 1,8-dioxo-octahydroxanthenes. To the best of our knowledge, there was only one example on the use of $HClO_4/SiO_2$ on the synthesis of 1,8-dioxo-octahydroxanthenes with a low yield.

In continuation of our work on the development of efficient protocols for the synthesis of xanthenes[38] an intermediate for the preparation of an antibacterial drug and in view of importance of heterogeneous acid catalysts in organic synthesis, we now wish to report that $HClO_4/SiO_2$ efficiently catalyzes synthesis of 1,8-dioxo-octahydroxanthenes. By the condensation of 5,5-dimethyl-1,3-cyclohexanedione(dimedone) **2** with wide variety of aromatic **1** aldehydes under solvent free conditions (Scheme **1**).



Scheme 1

RESULTS AND DISCUSSION

In continuation of our research on finding efficient and environmentally friendly catalysts for organic reactions[38-42] we came across a report on the use of $HClO_4/SiO_2$ catalyst in preparation of 1,8-dioxo-octahydroxanthenes[20] is claimed that the intermediate obtained is 2,2´-arylmethylene bis(3-hydroxy-5,5dimethyl-2-cyclohexene-1-one) **4** in 68% yield and the cyclized product **3** is obtained in 32% yield in the presence of 30 mol% of $HClO_4/SiO_2$.

We wish to dispute these results and present our findings which show the formation of cyclized products. We have used $HClO_4/SiO_2$ in condensation reaction of benzaldehydes **1** with dimedone **2** giving 1,8-dioxo-octahydroxanthenes **3** in excellent yields. In order to elucidate the structure of these compounds, we examined the structure of one compound (**3d**) by X-ray crystallography.[43] ORTEP (Oak Ridge Thermal Ellipsoid Plot) view of this structure (Figure **1**) shows the three rings in the molecule cyclized and 1,8-dioxo-octahydroxanthene fully formed.

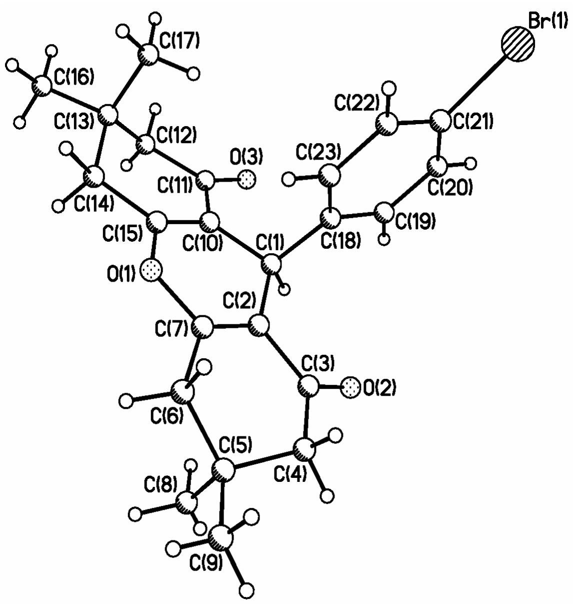


Figure 1. ORTEP view of the compound **3d**

In order to determine the optimal reaction conditions and evaluate the catalytic efficiency of $HClO_4/SiO_2$ catalyst, a model study was carried out on the synthesis of **3a** (Scheme **1**). Various solvents as well as solvent free conditions were tested and it was found that condensation of benzaldehyde with dimedone was proceeded to give the highest yield, under solvent free conditions (94% yield, 15 min).

Results in Table **1** show the generality of the reaction. The results also indicate that the reaction is not substituted sensitive. The yields obtained were good to excellent without formation of any side products giving xanthenediones **3** in 82-96% yields.

Table 1. Preparation of 1,8-dioxo-octahydroxanthenes **3** catalyzed by $HClO_4/SiO_2$ under solvent free conditions

Entry	Ar	Time (min)	Yield (%)[a]	Product	Mp (°C)	
					Found	Reported
1	C_6H_5	15	94	**3a**	204-205	202-204 [13]
2	4-ClC_6H_4	15	94	**3b**	225-226	228-230 [13]
3	2-ClC_6H_4	20	85	**3c**	228-230	228-230 [13]
4	4-BrC_6H_4	15	94	**3d**	233-235	234-236 [17]
5	4-FC_6H_4	15	96	**3e**	224-225	224-226 [17]
6	4-MeC_6H_4	18	92	**3f**	218-220	217-218 [13]
7	4-$MeOC_6H_4$	18	86	**3g**	243-245	242-244 [13]
8	2-$MeOC_6H_4$	20	85	**3h**	184-185	190-191 [44]
9	3-$MeOC_6H_4$	20	82	**3i**	177-180	---

10	2,4-$MeOC_6H_3$	20	85	**3j**	209-211	---
11	4-HOC_6H_4	18	85	**3k**	243-245	246-248 [14]
12	2-HOC_6H_4	20	82	**3l**	202-205	205-206 [44]
13	4-$O_2NC_6H_4$	15	94	**3m**	226-227	226-228 [13]
14	3-$O_2NC_6H_4$	20	92	**3n**	168-170	168-170 [13]
15	$C_6H_5CH=CH$	20	90	**3o**	177-178	175-177 [13]
16	2-naphthyl	15	92	**3p**	194-196	---

[a] Isolated yield.

All the products obtained were characterized by spectroscopic methods such as IR, ^1H NMR, for unknown compound (^{13}C NMR and analytical data) and also by comparison with the reported spectral data and melting points.

REUSABILITY OF CATALYST

To investigate the reusability and recycling of $HClO_4/SiO_2$. *p*-Bromobenzaldehyde, dimedone and 0.01 mmol $HClO_4/SiO_2$ were mixed in neat condition. The mixture was stirred at 80 °C. When the reaction was completed, the reaction mixture was dissolved in hot ethanol and catalyst was separated by simple filtration and recovered. $HClO_4/SiO_2$ was reused in subsequent reactions. No significant decrease in activity up to five runs was observed (Table **2**).

Table 2. The recycling of 0.01 mmol of $HClO_4/SiO_2$ in neat conditions

Entry	Time (min)	Yield(%)[a]
1	15	94
2	15	94
3	15	92
4	20	90
5	20	90

[a] Isolated yields.

EXPERIMENTAL

The products (**3a-r**) were isolated and characterized by comparison of physical and spectral data with those reported in literature. ^1H NMR and ^{13}C NMR spectra were recorded on Bruker Avance-300 MHz spectrometers with 7–10 mM solutions in $CDCl_3$ in the presence of tetramethylsilane as internal standard. IR spectra were recorded using a Perkin-Elmer 843 spectrometer with KBr plates. Melting points were determined on an Electro thermal 9100, and are not corrected.

PREPARATION OF $HClO_4/SiO_2$ CATALYST

70% Aqueous perchloric acid (1.8 g, 12.5 mmol) was added to a suspension of SiO_2 (230-400 mesh, 23.7 g) in ether (70 mL). The mixture was concentrated and the residue was heated at 100 °C for 72 h under vacuum to give $HClO_4/SiO_2$ (0.5 mmol/g) a free flowing powder (50 mg = 0.025 mmol of $HClO_4$).

GENERAL EXPERIMENTAL PROCEDURE

A solution of 1 mmol of aldehyde and 2 mmol of dimedone in CH_2Cl_2 (5 mL), was added the $HClO_4/SiO_2$ (20 mg, 0.01 mmol, 1 mol%) in a 20 mL glass vial. The solvent was allowed to evaporate and the dry residue was stirred at 80 °C for an appropriate time according to Table **1.** The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was dissolved in hot ethanol and the catalyst was separated by simple filtration. The filtrate was kept at rt to give the pure product.

The spectral (IR, ^1H NMR, ^{13}C NMR) and analytical data of unknown compounds are given below:

Compound 3i (Table 1): with solid; IR (KBr): ν_{max}/cm^{-1} 3005, 2959, 2873, 1674, 1660, 1625, 1605, 1584, 1486, 1447, 1360, 1274, 1201, 1164, 1139, 1047, 1001, 9001, 862, 801, 768, 691, 654, 574; ^1H NMR (300 MHz; $CDCl_3$; Me_4Si): δ 1.00 (s, 6H, $2CH_3$), 1.10 (s, 6H, $2CH_3$), 2.21 (ABq, 4H, J = 16.4 Hz, $2CH_2$, H-4, H-5), 2.45 (s, 4H, $2CH_2$, H-2, H-7), 3.77 (s, 3H, OCH_3), 4.74 (s, 1H, H-9), 6.63-6.67 (m, 1H, ArH), 6.86-6.89 (m, 2H, ArH), 7.10-7.15 (m, 1H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 27.41, 29.22, 31.76, 32.18, 40.85, 50.74, 55.09, 55.13, 111.80, 114.29, 115.54, 120.87, 128.87, 145.68, 159.31, 162.25, 196.39; Anal. Calcd for $C_{24}H_{28}O_4$: C, 69.33; H, 9.33. Found: C, 68.99; H, 9.41.

Compound 3j (Table 1): with solid; IR (KBr): ν_{max}/cm^{-1} 3019, 2967, 2890, 1679, 1667, 1628, 1613, 1589, 1508, 1468, 1429, 1364, 1301, 1272, 1217, 1201, 1170, 1140, 1048, 1005, 933, 836, 578; ^1H NMR (300 MHz; $CDCl_3$; Me_4Si): δ 0.95 (s, 6H, $2CH_3$), 1.09 (s, 6H, $2CH_3$), 2.18 (ABq, 4H, J = 16.4 Hz, $2CH_2$, H-4, H-5), 2.40 (ABq, 4H, J = 17.4 Hz, $2CH_2$, H-2, H-7), 3.72 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 4.77 (s, 1H, H-9), 6.32 (d, 1H, J = 2.3 Hz, ArH), 6.43 (m, 1H, ArH), 7.3 (d, 1H, J = 8.3 Hz ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.67, 29.05, 29.54, 32.12, 40.93, 50.78, 54.99, 55.12, 98.53, 103.91, 113.71, 123.14, 132.55, 158.42, 159.44, 162.78, 196.73; Anal. Calcd for $C_{25}H_{30}O_5$: C, 73.17; H, 7.32. Found: C, 73.26; H, 7.45.

Compound 3p (Table 1): with solid; IR (KBr): ν_{max}/cm^{-1} 3069, 2971, 2940, 2885, 1679, 1667, 1630, 1605, 1511, 1466, 1364, 1199, 1167, 1142, 1005, 829, 747, 484; ^1H NMR (300 MHz; $CDCl_3$; Me_4Si): δ 0.98 (s, 6H, $2CH_3$), 1.10 (s, 6H, $2CH_3$), 2.19 (ABq, 4H, J = 16.3 Hz, $2CH_2$, H-4, H-5), 2.51 (s, 4H, $2CH_2$, H-2, H-7), 4.92 (s, 1H, H-9), 7.36-7.40 (m, 2H, ArH), 7.44-7.47 (m, 1H, ArH), 7.69-7.75 (m, 4H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 27.32, 29.30, 31.98, 32.21, 40.89, 50.72, 115.59, 125.29, 125.58, 126.87, 127.13, 127.45, 127.68, 127.97, 132.34, 133.37, 141.62, 162.31, 196.40; Anal. Calcd for $C_{27}H_{28}O_3$: C, 81.00; H, 7.00. Found: C, 81.13; H, 7.07.

ACKNOWLEDGEMENTS

We thank the faculty of chemistry of Tarbiat Moalem University for supporting of this work.

REFERENCES

1. S. M. Menchen, S. C. Benson, J. Y. L. Lam, W. Zhen, D. Sun, B. B. Rosenblum, S. H. Kha, and M. Taing, *US Patent*, 2003, 6,583,168.
2. A. Banerjee and A. K. Mukherjee, *Stain Technol.*, 1981, **56**, 83.
3. G. A. Reynolds, S. A. Tuccio, O. G. Peterson, and D. P. Specht, *German Patent,* 1971, DE2109040.
4. H. Takeshika and T. Kijima, *Jpn. Tokkyo Koho*, 1981, JP56005480.
5. R. M. Ion, A. Planner, K. Wiktorowicz, and D. Frackowiak, *Acta Biochim. Pol.,* 1998, **45**, 833.
6. J. P. Poupelin, G. Saint-Ruf, O. Foussard-Blanpin, G. Narcisse, G. Uchida-Ernouf, and R. Lacroix, *Eur. J. Med. Chem.,* 1978, **13**, 67.
7. R. W. Lambert, J. A. Martin, J. H. Merrett, K. E. B. Parkes, and G. J. Thomas, *PCT Int. Appl.*, 1997, WO9706178
8. J.-Q. Wang and R. G. Harvey, *Tetrahedron,* 2002, **58**, 5927.
9. D. W. Knight and P. B. Little*, J. Chem. Soc., Perkin Trans.1,* 2001, **14**, 1771.
10. D. W. Knight and P. B. Little, *Synlett,* 1998, 1141.
11. G. Casiraghi, G. Casnati, and M. Cornia*, Tetrahedron Lett.,* 1973, **14**, 679.
12. G. Casiraghi, G. Casnati, M. Catellani, and M. Corina, *Synthesis,* 1974, 564.
13. T.-S. Jin, J.-S. Zhang, J.-C. Xio, A.-Q. Wang, and T.-S. Li, *Synlett,* 2004, 866.
14. T.-S. Jin, J.-S. Zhang, A.-Q. Wang, and T.-S. Li, *Ultrason. Sonochem.*, 2006, **13**, 220.
15. A. R. Khosropour, M. M. Khodaei, and H. Moghannian, *Synlett,* 2005, 955.
16. B. Das, P. Thirupathi, K. R. Reddy, B. Ravikanth, and L. Nagarapu, *Catal. Commun.,* 2007, **8**, 535.
17. Xuesen Fan, X. Hu, X. Zhang, and J. Wang, *Can. J. Chem.*, 2005, **83**, 16.
18. B. Das, P. Thirupathi, I. Mahender, V. S. Reddy, and Y. K. Rao, *J. Mol. Catal. A: Chem.*, 2006, **247**, 233.
19. A. John, P. J. P. Yadav, and S. Palaniappan*, J. Mol. Catal. A: Chem.*, 2006, **248**, 121.
20. S. Kantevari, R. Bantu, and L. Nagarapu, *J. Mol. Catal. A: Chem.,* 2007, **269**, 53. In the ref. 20 A mixture of dimedone, aldehyde and catalyst $HClO_4/SiO_2$ was heated at 140 °C but in this work for completely homogenousing we dissolve a mixture of aldehyde, dimedone and $HClO_4/SiO_2$ in CH_2Cl_2 as a solvent then the solvent was allowed to evaporate. After this process the reaction was done.
21. A. Corma and H. Garcia, *Adv. Synth. Catal.,* 2006, **348**, 1391.
22. A. K. Chakraborthi and R. Gulhane, *Chem. Commun.*, 2003, 1896.
23. V. T. Kamble, V. S. Jamode, N. S. Joshi, A. V. Biradar, and R. Y. Deshmukh, *Tetrahedron Lett.,*

2006, **47**, 5573.

24. A. T. Kahan, L. H. Choudhury, and S. Ghosh, *J. Mol. Catal. A: Chem.*, 2006, **255**, 230.
25. S. Rudrawar, R. C. Besra, and A. K. Chakraborti, *Synthesis*, 2006, 2767.
26. A. T. Khan, T. Pravin, and L. H. Choudhury, *Synthesis*, 2006, 2497.
27. A. Agarwal, and Y. D. Vankar, *Carbohydr. Res.*, 2005, **340**, 1661.
28. A. Agarwal, S. Rani, and Y. D. Vankar, *J. Org. Chem.*, 2004, **69**, 6140.
29. A. T. Khan, S. Ghosh, and L. H. Choudhury, *Eur. J. Org. Chem.*, 2006, 2226.
30. G. Agnihotri and A. K. Misra, *Tetrahedron Lett.*, 2006, **47**, 3653.
31. P. Tiwari and A. K. Misra, *Tetrahedron Lett.,* 2006, **47**, 3573.
32. M. Maheswara, V. Siddaiah, G. L. V. Damu, and C. V. Rao, *ARKIVOC*, 2006, 201.
33. V. T. Kamble, K. R. Kadam, N. S. Joshi, and D. B. Muley, *Catal. Commun.*, 2007, **8**, 498.
34. Y. Du, G. Wei, S. Cheng, Y. Hua, and R. J. Linhardt, *Tetrahedron Lett.*, 2006, **47**, 307.
35. A. K. Chakraborthi and S. V. Chankeshwara, *Org. Biomol. Chem.*, 2006, **4**, 2769.
36. S. Kantevari, S. V. N. Vuppalapati, D. O. Biradar, and L. Nagarapu, *J. Mol. Catal. A: Chem.*, 2007, **266**, 109.
37. M. Narasimhulu, T. S. Reddy, K. C. Mahesh, P. Prabhakar, C. B. Rao, and Y. Venkateswarlu, *J. Mol. Catal. A: Chem.,* 2007, **266**, 114.
38. M. A. Bigdeli, M. M. Heravi, and G. H. Mahdavinia, *Catal. Commun.*, 2007, **8**, 1595.
39. M. A. Bigdeli, S. Jafari, G. H. Mahdavinia, and H. Hazarkhani, *Catal. Commun.*, 2007, **8**, 1641.
40. M. A. Bigdeli, G. H. Mahdavinia, and S. Jafari, *J. Chem. Res.*, 2007, 26.
41. M. A. Bigdeli, M. M. Heravi, and G. H. Mahdavinia, *J. Mol. Catal. A: Chem.*, 2007, **275**, 25.
42. M. A. Bigdeli, G. H. Mahdavinia, S. Jafari, and H. Hazarkhani, *Catal. Commun.*, 2007, **8**, 2228.
43. M. A. Bigdeli, G. H. Mahdavinia, and V. Amani, *Acta Cryst. E63*, 2007, o3493.
44. E. C. Horning and M. G. Horing, *J. Org. Chem.,* 1946, **11**, 95.