Journal of Molecular Catalysis A: Chemical 367 (2013) 99–102

Contents lists available at SciVerse ScienceDirect

Journal of Molecular Catalysis A: Chemical

journal homepage: www.elsevier.com/locate/molcata

[Et_3NH][HSO_4] catalyzed efficient and green synthesis of 1,8-dioxo-octahydroxanthenes

Zhongqiang Zhou*, Xiaocui Deng

Key Laboratory of Catalysis and Materials Science of the State Ethnic Affairs Commission and Ministry of Education, Hubei Province, College of Chemistry and Materials Science, South-Central University for Nationalities, Wuhan 430074, China

ARTICLE INFO

Article history:
Received 8 May 2012
Received in revised form 28 October 2012
Accepted 1 November 2012
Available online 9 November 2012

Keywords:
1,8-Dioxo-octahydroxanthenes
[Et_3NH][HSO_4]
Solvent-free
Aromatic aldehydes
5,5-Dimethyl-1,3-cyclohexanedione

ABSTRACT

A simple and efficient procedure for synthesis of 1,8-dioxo-octahydroxanthenes by one-pot condensation of aromatic aldehydes with 5,5-dimethyl-1,3-cyclohexanedione under solvent-free conditions using ionic liquid [Et_3NH][HSO_4] as catalyst is described. The procedure offers several advantages including cleaner reaction profiles, use of easily available, cheap, recyclable and environmentally benign nature of catalyst, high yields, and simple experimental and work-up procedures.

1. Introduction

Xanthenes are an important family of organic compounds because they have wide range of biological and pharmaceutical properties such as anti-inflammatory [1], anti-depressants and antimalarial agents [2]. Furthermore, these compounds have been used as dyes [3], and pH-sensitive fluorescent materials for the visualization of biomolecular assemblies [4].

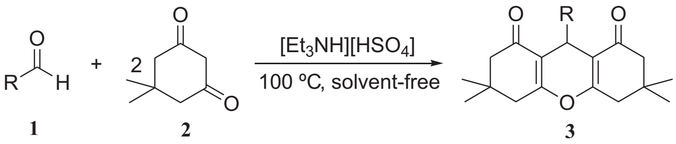
Many synthetic methods for preparing xanthenediones have been reported by the condensation of aromatic aldehydes and 5,5-dimethyl-1,3-cyclohexanedione in the presence of [1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2,2,2]octane bis(tetrafluoroborate) [5], montmorillonite K10 [6], *p*-dodecylbenzenesulphonic acid [7], alumina-sulfuric acid [8], trimethylsilyl chloride [9], $NaHSO_4$–SiO_2 [10], ZnO–acetyl chloride [11], PMA–SiO_2 [12], NBS [13], Amberlyst-15 [14], Dowex-50W [15], PPA–SiO_2 [16], $ZrOCl_2 \cdot 8H_2O$ [17], trichloroisocyanuric acid [18], silica sulfuric acid [19], heteropolyacid supported MCM-41 [20], silica bonded N-propyl sulfamic acid [21], nanosized MCM-41-SO_3H [22], [Bmim][HSO_4] [23,24], [Hmim]TFA [25], [TMPSA]HSO_4 [26], [DDPA][HSO_4] [27], [Et_3N-SO_3H]Cl [28] and [Hbim]BF_4 [29] as catalysts. Rahmati reported that the synthesis of xanthenedione derivatives could be proceeded in ionic liquid tetramethylguanidinium trifluoroacetate catalyzed by trifluoroacetate acid [30]. Fan et al. and Ma et al. reported that the synthesis of xanthenedione derivatives could be proceeded in ionic liquid [bmim]BF_4 catalyzed by $FeCl_3 \cdot 6H_2O$ [31], $InCl_3 \cdot 4H_2O$ [32], and $NaHSO_4$ [33], respectively. Each of these methods have their own advantages but also suffer from one or more disadvantages such as prolonged reaction time, low yields, use of hazardous or expensive catalysts, use of organic solvents, tedious work-up processes, the requirement of special apparatus, and difficulty in recovery and reusability of the catalysts. Thus, the search for the new readily available and green catalysts is still being actively pursued.

Ionic liquids have been turned to be a kind of promising alternative medium/catalysts for various chemical processes. Protic ionic liquids are easily produced through the combination of a Brønsted acid and Brønsted base [34]. Li reported that protic ionic liquid [Et_3NH][HSO_4] has been used as catalyst and environmentally benign solvent for the cracking reactions of dialkoxypropanes [35]. Recently, [Et_3NH][HSO_4] catalyzed electrophilic substitution reactions of indoles with various carbonyl compounds for the one pot efficient synthesis of bis(indolyl)methanes has also been reported [36]. Herein, we report a facile method for the synthesis of 1,8-dioxo-octahydroxanthenes by the condensation of aromatic aldehydes with 5,5-dimethyl-1,3-cyclohexanedione using easily

---

* Corresponding author. Tel.: +86 27 67842752; fax: +86 27 67842752.
E-mail address: zhou-zq@hotmail.com (Z. Zhou).

1381-1169/$ – see front matter © 2012 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.molcata.2012.11.002



Scheme 1. $[Et_3NH][HSO_4]$ catalyzed synthesis of 1,8-dioxo-octahydroxanthenes.

available, cheap, and reusable protic ionic liquid $[Et_3NH][HSO_4]$ as catalyst under solvent-free conditions (Scheme 1).

2. Experimental

2.1. Material and instruments

FT-IR spectra were obtained on a Nexus 470 spectrophotometer. ^1H NMR spectra were recorded on a Bruker Avance III 400 with TMS as internal standard. Melting points were determined on a melting point apparatus and are uncorrected.

2.2. Preparation of $[Et_3NH][HSO_4]$

Sulfuric acid (19.6 g, 0.2 mol) 98% solution in water was dropped into the triethylamine (20.2 g, 0.2 mol) under stirring at 60 °C in 1 h [35]. After the addition, the reaction mixture was stirred for an additional period of 1 h at 70 °C to ensure the reaction had proceeded to completion. Then the trace of water was removed by heating the residue at 80 °C in high vacuum until the weight of the residue remained constant.

2.3. General procedure for the synthesis of 1,8-dioxo-octahydroxanthenes under solvent-free conditions

To a mixture of aldehyde (**1**, 5 mmol) and 5,5-dimethyl-1,3-cyclohexanedione (**2**, 10 mmol), $[Et_3NH][HSO_4]$ (1 mmol) was added and the mixture was heated on an oil bath at 100 °C with good stirring. During the reaction process, the mixture spontaneously solidified up. The progress of the reaction was monitored by thin layer chromatography (ethyl acetate/hexane = 1/3). After completion of the reaction, the obtained solid was recrystallized from 95% ethanol to afford the desired compound in pure form. The mother liquor (consisting of 95% ethanol, ionic liquid $[Et_3NH][HSO_4]$, and some other residual reactants or byproducts) was further vacuumed to dryness and the resulting catalyst was reused directly for the next run. All the products are known compounds and were characterized by spectral data and comparison of their physical data with literature data.

2.4. General procedure for the synthesis of 1,8-dioxo-octahydroxanthenes under solvent conditions

A mixture of aldehyde (**1**, 5 mmol), 5,5-dimethyl-1,3-cyclohexanedione (**2**, 10 mmol) and $[Et_3NH][HSO_4]$ (1 mmol) in 5 mL of solvent was heated under reflux conditions for the specified time given in Table 1. After completion of the reaction, the organic solvent was evaporated, and the crude products were purified by crystallization from 95% ethanol.

3. Results and discussion

In order to optimize the reaction conditions, firstly, we investigated the effect of different solvents on the reaction rate and as well as yields of the products (Table 1). As a model reaction, the reaction of benzaldehyde (5 mmol) with 5,5-dimethyl-1,3-cyclohexanedione (10 mmol) catalyzed by $[Et_3NH][HSO_4]$ (1 mmol, 20 mol% relative to reactants) in various solvents including ethanol, benzene, chloroform, tetrahydrofurane, acetonitrile and water was investigated under reflux condition. The results were summarized in Table 1. In protic solvents such as ethanol, the reaction was very slow and resulted in lower product yield. Conducting the reactions in aprotic solvents such as benzene, chloroform, tetrahydrofurane and acetonitrile improved both the reaction rates as well as product yields. Water has been identified as an ideal solvent because it is inexpensive, non-flammable, abundant and environmentally benign. However, when the same reaction was carried out in water, the expected product was obtained only in trace amount after 2 h.

Solvent-free conditions make procedures simpler, save energy, and prevent solvent wastes, hazards, and toxicity. Furthermore, we conducted the condensation of benzaldehyde (5 mmol) and 5,5-dimethyl-1,3-cyclohexanedione (10 mmol) with stirring under solvent-free conditions. As shown in Table 1, the yields of the reaction under solvent-free conditions were higher and the reaction times were shorter than under solvent conditions.

To optimize the reaction temperature, the mixture was heated at different temperatures ranging from 20 to 110 °C. The yield of product **3** was increased when the reaction was raised from 20 to100 °C. However, no increase in the yield of product **3** was observed when the reaction temperature was raised from 100 to 110 °C.

Table 1
Effect of different reaction conditions on $[Et_3NH][HSO_4]$ catalyzed synthesis of 1,8-dioxo-octahydroxanthenes.[a]

Entry	Solvent	Temperature (°C)	Catalyst (mol%)	Time (min)	Yield[b] (%)
1	THF	Reflux	20	120	70
2	CH_3CN	Reflux	20	120	88
3	$CHCl_3$	Reflux	20	120	88
4	C_6H_6	Reflux	20	120	86
5	Ethanol	Reflux	20	120	54
6	Ethanol	Reflux	–	20 h	0 [13]
7	H_2O	Reflux	20	120	Trace
8	Solvent-free	20	20	120	45
9	Solvent-free	40	20	120	48
10	Solvent-free	60	20	120	77
11	Solvent-free	80	20	30	84
12	Solvent-free	80	–	15 h	41 [24]
13	Solvent-free	90	20	20	91
14	Solvent-free	100	20	20	94
15	Solvent-free	110	20	20	94
16	Solvent-free	100	5	20	90
17	Solvent-free	100	10	20	91
18	Solvent-free	100	30	20	93

[a] Reaction condition: benzaldehyde (5 mmol), 5,5-dimethyl-1,3-cyclohexanedione (10 mmol).
[b] Isolated yield.

Table 2
[Et$_3$NH][HSO$_4$] catalyzed synthesis of 1,8-dioxo-octahydroxanthenes.[a]

Entry	Aldehyde	Time (min)	Yield[b] (%)	Melting point (°C)	
				Found	Reported
1	Benzaldehyde	20	94	205–206	203–204 [24]
2	4-Tolualdehyde	25	96	207–208	208–209 [33]
3	4-Methoxybenzaldehyde	25	94	248–250	242–244 [24]
4	2-Chlorobenzaldehyde	20	90	225–226	225–227 [24]
5	4-Fluorobenzaldehyde	20	97	225–227	226–227 [17]
6	3-Methoxybenzaldehyde	40	94	183–184	177–180 [18]
7	4-Bromobenzaldehyde	45	87	240–241	240–241 [24]
8	3-Nitrobenzaldehyde	30	86	170–171	170–172 [24]
9	4-Hydroxy-3-methoxybenzaldehyde	30	87	224–227	226–228 [33]
10	4-Chlorobenzaldehyde	30	77	237–238	230–232 [24]
11	2,4-Dichlorobenzaldehyde	40	82	247–248	248–251 [17]
12	4-Nitrobenzaldehyde	30	92	226–228	225–227 [18]
13	2-Hydroxybenzaldehyde	20	83	203–205	202–205 [18]
14	4-Hydroxybenzaldehyde	20	84	250–251	248–250 [33]
15	Cinnamaldehyde	70	83	178–180	177–178 [13]

[a] Reaction condition: aromatic aldehyde (5 mmol), 5,5-dimethyl-1,3-cyclohexanedione (10 mmol), [Et$_3$NH][HSO$_4$] (1 mmol) at 100 °C under solvent-free conditions.
[b] Isolated yield.

Therefore, 100 °C was chosen as the reaction temperature for all further reactions.

To determine the optimum concentration of catalyst, we have investigated the model reaction at 5, 10, 20 and 30 mol% of [Et$_3$NH][HSO$_4$] at 100 °C under solvent-free conditions. The product was obtained in 90, 91, 94 and 93% yield, respectively. This indicates that 20 mol% of [Et$_3$NH][HSO$_4$] is sufficient for the best result. Subsequently, therefore, all reactions were carried out at 100 °C in the presence of 20 mol% of [Et$_3$NH][HSO$_4$] under solvent-free conditions.

Using these optimized reaction conditions, the scope and efficiency of this approach was explored for the synthesis of a wide variety of 1,8-dioxo-octahydroxanthenes and the obtained results are summarized in Table 2. It can be observed from Table 2 that several functionalities present in the aryl aldehydes such as halogen, methoxy and nitro group were tolerated. In all the cases the corresponding benzoxanthenes were obtained in good to excellent yield after 20–70 min. Thus, the aromatic aldehydes bearing both electron-donating and electron-withdrawing groups are desirable substrates for this reaction.

Subsequently, the reusability of [Et$_3$NH][HSO$_4$] was examined by using benzaldehyde as a model substrate under solvent-free conditions. After completion of the reaction, the obtained solid was recrystallized from 95% ethanol to afford the desired compound in pure form. The mother liquor (consisting of 95% ethanol, [Et$_3$NH][HSO$_4$], and some other residual reactants or byproducts) was vacuumed to remove solvent and the resulting catalyst was directly used in subsequent runs without further treatment. As can be seen from Table 3, the ionic liquid [Et$_3$NH][HSO$_4$] can be recycled at least six times without any loss of catalytic activity.

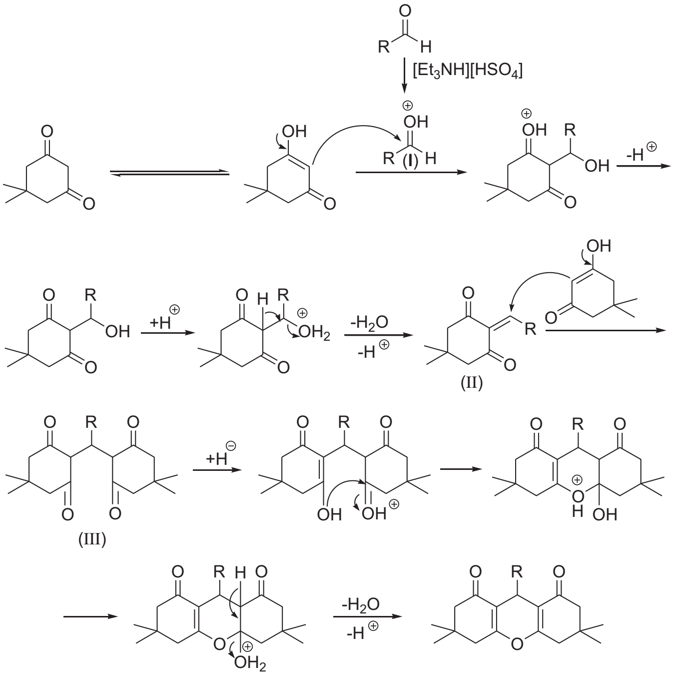
Table 3
Recycling of the [Et$_3$NH][HSO$_4$] catalyst.[a]

Run	Time (min)	Yield[b] (%)
1	20	94
2	20	94
3	20	94
4	20	94
5	20	95
6	20	95
7	20	96

[a] Reaction condition: benzaldehyde (5 mmol), 5,5-dimethyl-1,3-cyclohexanedione (10 mmol), [Et$_3$NH][HSO$_4$] (1 mmol) at 100 °C under solvent-free conditions.
[b] Isolated yield.

Finally, the efficiency of [Et$_3$NH][HSO$_4$] was compared with that of other ionic liquids reported earlier in the synthesis of 1,8-dioxo-octahydroxanthenes by one-pot condensation of aromatic aldehydes with 5,5-dimethyl-1,3-cyclohexanedione. The data summarized in Table 4 show the promising feature of this method in terms of reaction rate and the yield of product compared with those reported in the literature. Additionally, the present catalyst seems to be more beneficial from the economical and accessibility point of view.

A plausible mechanism for the synthesis of 1,8-dioxo-octahydroxanthenes catalyzed by [Et$_3$NH][HSO$_4$] is shown in Scheme 2. We propose that one molecule of 5,5-dimethyl-1, 3-cyclohexanedione was firstly condensed with an activated aldehyde [I] to afford intermediate [II]. Then another molecule of 5,5-dimethyl-1,3-cyclohexanedione reacted with [II] via Michael addition reaction to give the intermediate [III]. Finally,



Scheme 2. Plausible mechanism for the synthesis of 1,8-dioxo-octahydroxanthenes catalyzed by [Et$_3$NH][HSO$_4$].

Table 4
Comparison of ionic liquids used as catalysts for the synthesis of 1,8-dioxo-octahydroxanthenes.[a]

Entry	Ionic liquid	Conditions	Time (min)	Yield (%)	Reference
1	[Bmim][HSO_4]	Solvent-free, 100 °C	25	93	[23]
2	[Bmim][HSO_4]	Solvent-free, 80 °C	180	85	[24]
3	[Hmim]TFA	Solvent-free, 80 °C	180	85	[25]
4	[TMPSA]HSO_4	H_2O, 100 °C	60	94	[26]
5	[DDPA][HSO_4]	H_2O, 100 °C	60	93	[27]
6	[Et_3N-SO_3H]Cl	Solvent-free, 80 °C	60	97	[28]
7	[Hbim]BF_4	Ultrasonication, rt, MeOH	45	85	[29]
8	[Et_3NH][HSO_4]	Solvent-free, 100 °C	20	94	Present work

[a] Based on benzaldehyde.

cyclodehydration of the intermediate [III] gave the expected products 1,8-dioxo-octahydroxanthenes.

4. Conclusion

In summary, we developed a simple, efficient and eco-friendly procedure for synthesis of 1,8-dioxo-octahydroxanthenes by one-pot condensation of aromatic aldehydes with 5,5-dimethyl-1,3-cyclohexanedione under solvent-free conditions using ionic liquid [Et_3NH][HSO_4] as catalyst. The procedure offers several advantages including cleaner reaction profiles, use of easily available, cheap, recyclable and environmentally benign nature of catalyst, high yields, and simple experimental and work-up procedures.

Acknowledgements

We thank the Natural Science Foundation of Hubei Province (grant No. 2007ABA291) for financial support.

References

[1] J.P. Poupelin, G. Saint-Rut, O. Fussard-Blanpin, G. Narcisse, G. Uchida-Ernouf, R. Lakroix, Eur. J. Med. Chem. 13 (1978) 67–71.

[2] K. Chibale, M. Visser, D.V. Schalkwyk, P.J. Smith, A. Saravanamuthu, A.H. Fairlamb, Tetrahedron 59 (2003) 2289–2296.

[3] A. Banerjee, A.K. Mukherjee, Stain. Technol. 56 (1981) 83–85.

[4] C.G. Knight, T. Stephens, J. Biochem. 258 (1989) 683–687.

[5] M.R.P. Heravi, J. Iran Chem. Soc. 6 (2009) 483–488.

[6] M. Dabiri, S.C. Azimi, A. Bazgir, Chem. Pap. 62 (2008) 522–526.

[7] T. Jin, J. Zhang, J. Xiao, A. Wang, T. Li, Synlett (2004) 0866–0870.

[8] A. Pramanik, S. Bhar, Catal. Commun. 20 (2012) 17–24.

[9] S. Kantevari, R. Bantu, L. Nagarapu, ARKIVOC 2006 Part (xvi) (2006) 136–148.

[10] B. Dashttp, P. Thirupathi, K.R. Reddy, B. Ravikanth, L. Nagarapu, Catal. Commun. 8 (2007) 535–538.

[11] M.T. Maghsoodlou, S.M. Habibi-Khorassani, Z. Shahkarami, N. Maleki, M. Rostamizadeh, Chin. Chem. Lett. 21 (2010) 686–689.

[12] P. Srihari, S.S. Mandal, J.S.S. Reddy, R.S. Rao, J.S. Yadav, Chin. Chem. Lett. 19 (2008) 771–774.

[13] G.H. Mahdavinia, J. Iran Chem. Res. 1 (2008) 11–17.

[14] B. Das, P. Thirupathi, I. Mahender, V.S. Reddy, Y.K. Rao, J. Mol. Catal. A: Chem. 247 (2006) 233–239.

[15] G.I. Shakibaei, P. Mirzaei, A. Bazgir, Appl. Catal. A: Gen. 325 (2007) 188–192.

[16] S. Kantevari, R. Bantu, L. Nagarapu, J. Mol. Catal. A: Chem. 269 (2007) 53–57.

[17] H. Lü, J. Li, Z. Zhang, Appl. Organometal. Chem. 23 (2009) 165–169.

[18] M.A. Bigdeli, F. Nemati, G.H. Mahdavinia, H. Doostmohammadi, Chin. Chem. Lett. 20 (2009) 1275–1278.

[19] M. Seyyedhamzeh, P. Mirzaei, A. Bazgir, Dyes Pigments 76 (2008) 836–839.

[20] G. Karthikeyan, A. Pandurangan, J. Mol. Catal. A: Chem. 311 (2009) 36–45.

[21] F. Rashedian, D. Saberi, K. Niknam, J. Chin. Chem. Soc. 57 (2010) 998–1006.

[22] S. Rostamizadeh, A.M. Amani, G.H. Mahdavinia, G. Amiri, H. Sepehrian, Ultrason. Sonochem. 17 (2010) 306–309.

[23] J. Ma, C. Wang, Q. Wu, R. Tang, H. Liu, Q. Li, Heteroatom. Chem. 19 (2008) 609–611.

[24] K. Niknam, M. Damya, J. Chin. Chem. Soc. 56 (2009) 659–665.

[25] M. Dabirir, M. Baghbanzadeh, E. Arzroomchilar, Catal. Commun. 9 (2008) 939–942.

[26] D. Fang, K. Gong, Z. Liu, Catal. Lett. 127 (2009) 291–295.

[27] D. Fang, J. Yang, Z. Liu, J. Heterocyclic Chem. 48 (2011) 468–472.

[28] A. Zare, A.R. Moosavi-Zare, M. Merajoddin, M.A. Zolfigol, T. Hekmat-Zadeh, A. Hasaninejad, A. Khazaei, M. Mokhlesi, V. Khakyzadeh, F. Derakhshan-Panah, M.H. Beyzavi, E. Rostami, A. Arghoon, R. Roohandeh, J. Mol. Liq. 167 (2012) 69–77.

[29] K. Venkatesan, S.S. Pujari, R.J. Lahoti, K.V. Srinivasan, Ultrason. Sonochem. 15 (2008) 548–553.

[30] A. Rahmati, Chin. Chem. Lett. 21 (2010) 761–764.

[31] X. Fan, Y. Li, X. Zhang, X. Hu, J. Wang, Chin. J. Org. Chem. 25 (2005) 1482–1486.

[32] X. Fan, X. Hu, X. Zhang, J. Wang, Can. J. Chem. 83 (2005) 16–20.

[33] J. Ma, J. Li, R. Tang, X. Zhou, Q. Wu, C. Wang, M. Zhang, Q. Li, Chin. J. Org. Chem. 27 (2007) 640–642.

[34] T.L. Greaves, C.J. Drummond, Chem. Rev. 108 (2008) 206–237.

[35] C. Wang, L. Guo, H. Li, Y. Wang, J. Weng, L. Wu, Green Chem. 8 (2006) 603–607.

[36] A. Rajendran, D. Raghupathy, M. Priyadarshini, Int. J. Chem. Tech. Res. 3 (2011) 298–302.