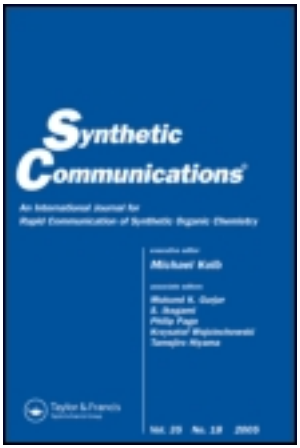


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

$CeCl_3 \cdot 7H_2O$-Catalyzed Synthesis of 1-Oxo-hexahydroxanthene Derivatives in Aqueous Media

Gowravaram Sabitha [a], K. Arundhathi [a], K. Sudhakar [a], B. S. Sastry [b] & J. S. Yadav [a]

[a] Organic Division I, Indian Institute of Chemical Technology, Hyderabad, India

[b] Univesity College of Pharmaceutical Sciences, Andhra University, Vizag, India

Version of record first published: 29 Sep 2008

To cite this article: Gowravaram Sabitha, K. Arundhathi, K. Sudhakar, B. S. Sastry & J. S. Yadav (2008): $CeCl_3 \cdot 7H_2O$-Catalyzed Synthesis of 1-Oxo-hexahydroxanthene Derivatives in Aqueous Media, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 38:20, 3439-3446

To link to this article: http://dx.doi.org/10.1080/00397910802154253

Synthetic Communications®, 38: 3439–3446, 2008

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910802154253

Taylor & Francis
Taylor & Francis Group

$CeCl_3 \cdot 7H_2O$-Catalyzed Synthesis of 1-Oxo-hexahydroxanthene Derivatives in Aqueous Media

Gowravaram Sabitha,[1] K. Arundhathi,[1] K. Sudhakar,[1] B. S. Sastry,[2] and J. S. Yadav[1]

[1]Organic Division I, Indian Institute of Chemical Technology, Hyderabad, India
[2]Univesity College of Pharmaceutical Sciences, Andhra University, Vizag, India

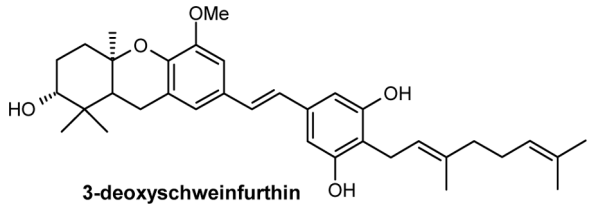
Abstract: Cerium(III) chloride heptahydrate ($CeCl_3 \cdot 7H_2O$) catalyzes the reaction of substituted salicylaldehydes with 1,3-cyclohexane dione or dimedone in aqueous medium at reflux temperature to afford the corresponding 1-oxo-1,2,3,4,9,10-hexahydroxanthene derivatives4 0 in high yields.

Keywords: $CeCl_3 \cdot 7H_2O$, 1, 3-cyclohexane dione, dimedone, hexahydroxanthenes, salicylaldehyde

INTRODUCTION

Xanthone derivatives are parent compounds of a large number of naturally occurring, as well as synthetic derivatives, and they occupy a prominent position in medicinal chemistry.[1] A new hexahydroxanthene derivative, vedelianin, has been extracted from the leaves of *Macaranga vedeliana*.[2] Hexahydroxanthenes are not abundant in nature, but they are a key feature in the schweinfurthins and some related natural products such as ugonstilbene, ugonin L, and cymobarbatol. The anticancer activity of the schweinfurthins, together with the difficulties encountered in efforts at repeated

Received March 3, 2008.
Address correspondence to Gowravaram Sabitha, Organic Division I, Indian Institute of Chemical Technology, Hyderabad 500 007, India. E-mail: gowravaramsr@yahoo.com



3-deoxyschweinfurthin

isolation, has drawn attention to their synthesis. The reports for the synthesis of hexahydroxanthene derivatives are rare.[3] Because of their biological importance, there is still demand for the synthesis of hexahydroxanthenes under mild conditions. In recent decades, chemists have begun investigating the possibility of using water as a solvent for organic reactions, with sometimes surprising and unforeseen results. The fact is that water is the cheapest, safest, and most non toxic solvent in the world. Some organic transformations that can be performed efficiently in aqueous solvent are the Diels–Alder reaction, Claisen rearrangements,[4] aldol reactions,[5],[6] allylation reactions,[7–9] and oxidations[10–12] and hydrogenations[13] of alkenes, to mention a few. Recently, $CeCl_3{\cdot}7H_2O$ has received attention as a cost-effective, nontoxic, readily available, and selective reagent for various organic transformations.[14] The mild Lewis acidity associated with cerium(III) chloride enhances its use at levels from stoichiometric to catalytic, and it is a powerful reagent for several organic reactions.[15] To the best of our knowledge, the synthesis of hexahydroxanthene derivatives has not reported using $CeCl_3{\cdot}7H_2O$.

Therefore, we report a new synthesis of 1-oxo-hexahydroxanthene derivatives using a catalytic amount of $CeCl_3{\cdot}7H_2O$ in aqueous medium. Thus, refluxing a mixture of 1 eq of salicilaldehyde **1** with 2 eq of 1,3-cyclohexane dione **2a** in the presence of a catalytic amount of $CeCl_3{\cdot}7H_2O$ in water afforded the corresponding hexahydroxanthene **3a** in 90% yield after recrystallization from 95% EtOH.

Similarly, various substituted salicylaldehydes reacted smoothly with cyclohexanedione, resulting in good yields of products. Dimedone also reacted well with substituted salicylaldehydes, affording the corresponding products in high yields, and the results are indicated in Table 1. The crude products were purified by recrystallization from 95% EtOH. All the products were characterized by IR, ^{1}H NMR, and mass spectral analysis and also by comparision with authentic samples.

In summary, we have demonstrated a simple, efficient, and practical synthesis of 1-oxo-1,2,3,4,9,10-hexahydroxanthene derivatives using $CeCl_3{\cdot}7H_2O$ as a catalyst in aqueous media. The use of inexpensive and readily available $CeCl_3{\cdot}7H_2O$ makes this procedure simple, convenient, and practical. The advantages are easy work up with high yields, cleaner reactions, short reaction times, and a nontoxic catalyst.

Table 1. $CeCl_3 \cdot 7H_2O$-catalyzed synthesis of 1-oxo-hexehydroxanthenes[a,b] in aqueous media

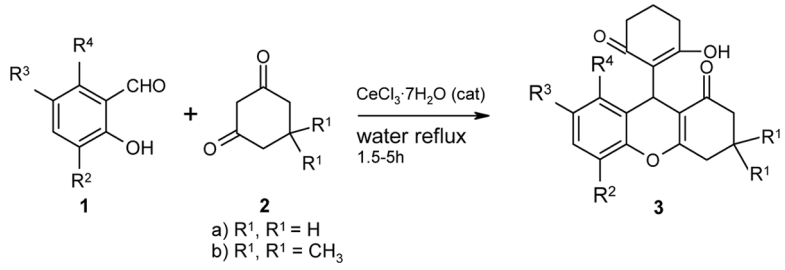
Entry	R^1	R^2	R^3	R^4	Time (h)	Yield (%)	Mp(°C)
3a	H	H	H	H	4	82	226
3b	H	H	Cl	H	3	87	220
3c	H	H	Br	H	3	91	219
3d	H	FOMe	H	H	4	86	232
3e	H	Br	t-Butyl	H	3	85	201
3f	H	t-Butyl	t-Butyl	H	3	82	211
3g	CH_3	H	H	H	3	92	204
3h	CH_3	H	Cl	H	3	96	228
3i	CH_3	H	Br	H	3	94	231
3j	CH_3	OMe	H	H	4	90	222
3k	CH_3	Br	t-Butyl	H	3	83	212
3l	CH_3	t-Butyl	t-Butyl	H	3	82	216

[a]All products were characterized by spectral data and compared with authentic samples.

[b]Isolated pure products.

EXPERIMENTAL

Melting points were determined using a Buchi R-535 apparatus and are uncorrected. All reactions were monitored by thin-layer chromatography (TLC) using silica-coated plates and visualization under UV light. Light petroleum of the distillation range 60–80 °C was used. Yields refer to pure products isolated by recrystallization and spectroscopically (^{1}H, IR) homogeneous material. ^{1}H NMR spectra were recorded on Varian FT 200-MHz (Gemini) and Bruker UXNMR FT 300-MHz (Avance) instruments in $CDCl_3$. Chemical shift values were reported in parts per million (δ) relative to tetramethylsilane (TMS)



Scheme 1.

(δ 0.0) as an internal standard. Mass spectra were recorded under electron impact at 70 eV on an LC-MSD (Agilent Technologies). EtOH 95% was used for recrystallization.

General Procedure

A mixture of 1 eq of substituted salicylaldehyde (**1**) and 2 eq of cyclohexane1,3-dione or dimedone (**2a or 2b**) in the presence of ceriumtrichloride heptahydrate in a small amount of water was stirred at 90 °C for 1.5–5 h. The crude product was collected by filtration, washed with water, dried, and purified by recrystallization from 95% EtOH to give 1-oxo-1,2,3,4,9,10-hexahydroxanthene derivatives (**3**) in high yields (see Table 1). The structure of the products was confirmed by spectral data (^{1}H NMR, IR, mass).

Spectral Data

Compound 3a

Mp 226 °C; IR (KBr): 3150, 2920, 2880, 1640, 1570, 1550, 1485, 1440. 1360, 1280, 1220, 1180, 1051, 991, 970, 905, 840 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): 1.92–2.75 (m, 12H, $6CH_2$), 4.60 (s, 1H, CH), 6.98–7.05 (m, 3H, ArH), 7.01–7.20 (m, 1H, ArH), 10.81 (s, 1H, OH); ESI MS: m/z 310 (M^+).

Compound 3b

Mp 220 °C; IR (KBr): 3110, 2989, 2884, 1675, 1642, 1580, 1481, 1376, 1219, 1210, 1186, 1072, 982, 810, 764 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): 1.84–2.82 (m, 12H, $6CH_2$), 4.64 (s, 1H, CH), 6.94 (d, $J = 8.4$ Hz, 1H, ArH), 7.09 (d, $J = 2.4$ Hz, 1H, ArH), 7.54 (dd, $J = 8.4$ Hz, $J = 2.4$ Hz, 1H, ArH), 10.56 (s, 1H, OH); ESI MS: m/z 367 ($M^+ + Na$).

Compound 3c

Mp 219 °C: IR (KBr): 3112, 2950, 2884, 1676, 1650, 1598, 1481, 1370, 1271, 1219, 1188, 1070, 982, 910, 820, 765 cm^{-1}; ^{1}H NMR (200 MHz $CDCl_3$): 1.91–2.78 (m, 12H, $6CH_2$), 4.50 (s, 1H, CH), 6.93 (d, $J = 8.4$ Hz, Hz, 1H, ArH), 7.20 (d, $J = 2.4$ Hz, 1H, ArH), 7.32 (dd, $J = 8.4$ Hz, $J = 2.4$ Hz, 1H, ArH), 10.71 (s, 1H, OH); ESI MS: m/z (%) 389 (M^+).

Compound 3d

Mp 232 °C: IR (KBr): 3220, 2956, 2884, 1672, 1650, 1598, 1482, 1370, 1271, 1219, 1198, 1070, 982, 910, 820, 765 $cm^{-1;}$ ^1H NMR (200 MHz, $CDCl_3$): 1.81–2.74 (m, 12H, $6CH_2$), 3.82 (s, 3H, OCH_3), 4.50 (s, 1H, CH), 6.80 (d, $J = 8.3$ Hz, 3H, ArH), 11.81 (s, 1H, OH); ESI MS: m/z 340 (M^+).

Compound 3e

Mp 201 °C: IR (KBr): 3210, 2950, 2890, 1680, 1640, 1598, 1480, 1370, 1221, 1186, 1076, 984, 810, 760 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 1.16 (s, 6H, $2CH_3$), 1.21 (s, 3H, CH_3), 1.93–2.77 (m, 12H, $6CH_2$), 4.62 (s, 1H, CH), 7.06–7.22 (m, 2H, ArH), 10.71 (s, 1H, OH); ESI MS: m/z 446 ($M^+ + 1$).

Compound 3f

Mp 211 °C: IR (KBr): 3110, 2942, 2890, 1670, 1636, 1598, 1456, 1370, 1210, 1185, 1078, 984, 810, 760 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): 1.18 (s, 12H, $4CH_3$), 1.22 (s, 6H, $2CH_3$), 1.92–2.78 (m, 12H, $6CH_2$), 4.68 (s, 1H, CH), 7.10–7.25 (m, 2H, ArH), 10.82 (s, 1H, OH); ESI MS: m/z 443 ($M^+ + Na$).

Compound 3g

Mp 204 °C: IR (KBr): 3182, 2951, 2860, 1652, 1591, 1481, 1372, 1320, 1246, 1185, 1140, 1013, 985, 810, 756 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 1.01 (s, 3H, CH_3), 1.04 (s, 6H, $2CH_3$), 1.12 (s, 3H, CH_3), 1.96–2.72 (m, 8H, $4CH_2$), 4.62 (s, 1H, CH), 6.98–7.22 (m, 4H, ArH), 10.40 (s, 1H, OH); ESI MS: m/z 366 (M^+).

Compound 3h

Mp 228 °C: IR (KBr): 3184, 2960, 2862, 1650, 1596, 1481, 1460, 1371, 1313, 1247, 1188, 1016, 985, 810, 755 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 0.98 (s, 3H, CH_3), 1.06 (s, 6H, $2CH_3$), 1.13 (s, 3H, CH_3), 1.94–2.56 (m, 8H, $4CH_2$), 4.63 (s, 1H, CH), 6.93 (d, $J = 8.8$ Hz, 1H, ArH), 6.99 (d, $J = 2.4$ Hz, 1H, ArH), 7.10 (dd, $J = 8.8$ Hz, $J = 2.4$ Hz, 1H, ArH), 10.41 (s, 1H, OH); ESI MS: m/z 400 (M^+).

Compound 3i

Mp 231 °C: IR (KBr): 3121, 2962, 2873, 1619, 1561, 1477, 1372, 1294, 1229, 1178, 1152, 1070, 1032, 886, 819 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): 0.99 (s, 3H, CH_3), 1.04 (s, 6H, $2CH_3$), 1.11 (s, 3H, CH_3), 1.98–2.60 (m, 8H, $4CH_2$), 4.61 (s, 1H, CH), 6.93 (d, $J = 8.4$ Hz, 1H, ArH), 7.12 (d, $J = 2.4$ Hz, 1H, ArH), 7.19 (dd, $J = 8.4$ Hz, $J^1 = 2.4$ Hz, 1H, ArH), 10.52 (s, 1H, OH); ESI MS: m/z (%) 446 ($M^+ + 1$).

Compound 3j

Mp 222 °C: IR (KBr): 3120, 2960, 2876, 1620, 1562, 1475, 1372, 1296, 1222, 1178, 1152, 1077, 1030, 888, 819 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 0.98 (s, 3H, CH_3), 1.02 (s, 6H, $2CH_3$), 1.10 (s, 3H, CH_3), 1.99–2.75 (m, 8H, $4CH_2$), 3.78 (s, 3H, O CH_3), 4.64 (s, 1H, CH), 6.93 (d, $J = 8.4$ Hz, 1H, ArH), 7.13 (d, $J = 7.55$ Hz, 2H, ArH), ESI MS: m/z 396 (M^+).

Compound 3k

Mp 212 °C: IR (KBr): 3122, 2982, 2874, 1620, 1560, 1450, 1372, 1295, 1220, 1176, 1152, 1070, 1032, 886, 820, 726 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 0.99 (s, 3H, CH_3), 1.06 (s, 6H, $2CH_3$), 1.12 (s, 9H, $3CH_3$), 1.16 (s, 3H, CH_3), 1.96–2.62 (m, 8H, $4CH_2$), 4.60 (s, 1H, CH), 6.98–7.23 (m, 2H, ArH), 10.52 (s, 1H, OH); ESI MS: m/z 502 ($M^+ + 1$).

Compound 3l

Mp 216 °C: IR (KBr): 3126, 2981, 2872, 1620, 1564, 1444, 1376, 1298, 1222, 1178, 1152, 1070, 1032, 889, 824, 726 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): 0.94 (s, 3H, CH_3), 1.02 (s, 6H, $2CH_3$), 1.06 (s, 9H, $3CH_3$), 1.09 (s, 9H, $3CH_3$), 1.12 (s, 3H, CH_3), 1.94–2.68 (m, 8H, $4CH_2$), 4.64 (s, 1H, CH), 6.98–7.25 (m, 2H, ArH), 10.52 (s, 1H, OH); ESI MS: m/z 478 (M^+).

ACKNOWLEDGMENT

K. S. thanks University Grants Commission, New Delhi, for the award of a fellowship.

REFERENCES

1. (a) Robak, J.; Gryglewski, R. J. Bioactivity of flavonoids. *Pol. J. Pharmacol.* **1996**, *48*, 55; (b) Wang, H. K.; Morris-Natschke, S. L.; Lee, K. H. Recent

advances in the discovery and development of topoisomerase inhibitors as antitumor agents. *Med. Res. Rev.* **1997**, *17*, 367; (c) Rukavishnikov, A. V.; Smith, M. P.; Birrell, G. B.; Keana, J. F. W.; Griffith, O. H. Synthesis of a new fluorogenic substrate for the assay of phosphoinositide-specific phospholipase C. *Tetrahedron Lett.* **1998**, *39*, 6637.

2. Thoison, O.; Hnawia, E.; Gueritte Voegelein, F.; Sevenet, T. Vedelianin, a hexahydroxanthene derivative isolated from *Macaranga vedeliana*. *Phytochemistry* **1992**, *31*(4), 1439–1442.
3. Wang, X.-S.; Shi, D.-Q.; Li, Y.-l.; Chen, H.; Wei, X.-Y.; Zong, Z.-M. A clean synthesis of 1-oxo-hexahydroxanthene derivatives in aqueous medium catalyzed by TEBA. *Synth. Commun.* **2005**, *35*, 97–104, and references cited therein.
4. Gajewski, J. J. In *Organic Synthesis in Water*; P. A. Grieco (Ed.); Blackie Academic & Professional: London, 1998.
5. Fringuelli, F.; Piermatti, O.; Pizzo, F. In *Organic Synthesis in Water*; P. A. Grieco (Ed.); Blackie Academic & Professional: London, 1998.
6. Kobayashi, S. In *Organic Synthesis in Water*; P. A. Grieco (Ed.); Blackie Academic & Professional: London, 1998.
7. Lu, W.; Chan, T. H. Indium-mediated organometallic reactions in aqueous media. Stereoselectivity in the crotylation of sulfonimines bearing a proximal chelating group. *J. Org. Chem.* 2001, *66*, 3467.
8. Loh, T.-P.; Zhou, J.-R. An enantioselective allylation reaction of aldehydes in an aqueous medium. *Tetrahedron Lett*. **1999**, *40*, 9115.
9. Li, C.-J.; Chan, T.-H. Organic syntheses using indium-mediated and catalyzed reactions in aqueous media. *Tetrahedron* **1999**, *55*, 11149.
10. Fokin, V. V.; Sharpless, K. B. A practical and highly efficient aminohydroxylation of unsaturated carboxylic acids. *Angew. Chem., Int. Ed. Engl.* **2001**, *40*, 3455.
11. Johnson, R. A.; Sharpless, K. B. In *Catalytic Asymmetric Synthesis*; I. Ojima (Ed.); VCH: Weinheim, 2000.
12. Frohn, M.; Shi, Y. Chiral ketone-catalyzed asymmetric epoxidation of olefins. *Synthesis* 2000, 1979.
13. Cornils, B.; Herrmann, W. A. *Aqueous Phase Organometallic Catalysis—Concept and Applications; Wiley-VCH: Weinheim, 1998.*
14. Imamoto, T. *Lanthanides in Organic Synthesis*; Academic Press: New York, 1994.
15. (a) Cappa, A.; Marcantoni, E.; Torregiani, E.; Bartoli, G.; Bellucci, M. C.; Bosco, M.; Sambri, L. A simple method for the selective deprotection of *p*-methoxybenzyl ethers by cerium(III) chloride heptahydrate and sodium iodide. *J. Org. Chem*. 1999, *64*, 5696–5699; (b) Di Dea, M.; Marcantoni, E.; Torregiani, E.; Bartoli, G.; Bellucci, M. C.; Bosco, M.; Sambri, L. A simple, efficient, and general method for the conversion of alcohols into alkyl iodides by a $CeCl_3 \cdot 7H_2O$/NaI system in acetonitrile. *J. Org. Chem.* **2000**, *65*, 2830–2833.
16. (a) Sabitha, G.; Rao, V. R. S.; Sudhakar, K.; Raj kumar, M.; Reddy, E. V.; Yadav, J. S. Study of conventional versus microwave-assisted reactions of

3,4-epoxyalcohols by $CeCl_3 \cdot 7H_2O$: Synthesis of tetrahydrofurans and 1-chloro-3-substituted-2-propanols. *J. Mol. Cat*. **2008**, *280*, 16–19; (b) Sabitha, G.; Babu, R. S.; Kumar, M. R.; Reddy, Ch. S.; Yadav, J. S. Highly regioselective ring opening of epoxides and aziridines using cerium(III) chloride. *Tetrahedron. Lett.* **2001**, *42*, 3955; (c) Sabitha, G.; Babu, R. S.; Kumar, M. R.; Reddy, Ch. S.; Yadav. J. S. Cerium(III) Chloride promoted highly regioselective ring opening of epoxides and aziridines using NaN_3 in acetonitrile: A facile synthesis of 1,2-azidoalcohols and 1,2-azidoamines. *Org. Lett.* **2002**, *4*, 343; (d) Sabitha, G.; Satheesh Babu, R.; Rajkumar, M.; Srividya, R.; Yadav, J. S. A highly efficient, mild, and selective cleavage of *β*-methoxyethoxymethyl (MEM) ethers by cerium(III) chloride in acetonitrile. *Org. Lett.* **2001**, *3*, 1149.