Tetrahedron 67 (2011) 3698–3704

Contents lists available at ScienceDirect

Tetrahedron

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

An efficient one-pot solvent-free synthesis and photophysical properties of 9-aryl/alkyl-octahydroxanthene-1,8-diones

Girijesh K. Verma, Keshav Raghuvanshi, Rajiv K. Verma, Pratibha Dwivedi, M.S. Singh *

Department of Chemistry, Faculty of Science, Banaras Hindu University, Varanasi 221005, U.P., India

ARTICLE INFO

Article history:
Received 15 January 2011
Received in revised form 7 March 2011
Accepted 22 March 2011
Available online 30 March 2011

Keywords:
One-pot synthesis
Tetramethyloctahydroxanthene-1,8-diones
Dimedone
Aldehydes
Indium trichloride
P_2O_5
Solvent-free condition
Optical behavior

ABSTRACT

A facile and efficient protocol for the synthesis of 9-aryl/alkyl-3,3,6,6-tetramethyl-1,2,3,4,5,6,7,8-octahydroxanthene-1,8-diones has been developed by one-pot reaction of dimedone with aldehydes in the presence of $InCl_3$ or P_2O_5 under solvent-free conditions. The optical behaviors of the xanthenediones have been investigated by UV–vis and fluorescence spectroscopy. The present approach offers the advantages of simple methodology, clean and mild reaction, high atom-economy, short reaction time, low environmental impact, wide substrate scope, high yield, and excellent purity.

1. Introduction

There are a number of environmental implications of the use of a large volume of organic solvents since they are utilized in larger quantities than the solutes they carry, and are wasted into the environment through evaporation and leakage. Because of the increasing concern for the harmful effects of organic solvents on the environment and human body, organic reactions that are operated without conventional organic solvents have aroused attention of organic chemists. Many organic reactions have been reported to proceed efficiently under solvent-free conditions and sometimes show enhanced selectivity[1] also. Therefore, more and more chemist's synthetic endeavors are devoted toward nature friendly synthesis[2a] to reduce drastic prerequisites for reactions. Among the proposed solutions, solvent-free conditions hold a leading position. So, it is now often claimed that 'the best solvent is no solvent'.[2b]

Xanthenes are important classes of organic compounds of a large number of naturally occurring as well as synthetic derivatives, and occupy a prominent position in medicinal chemistry.[3] They are important biologically active heterocyclic compounds possessing antiviral,[4] anti-inflammatory,[5] and antibacterial[6] activities. These are being utilized as antagonists for paralyzing action of zoxazolamine[7] and in photodynamic therapy.[8] Furthermore, these compounds can be used as dyes,[9] in laser technologies,[10] and as pH sensitive fluorescent materials for visualization of biomolecules.[11] In particular, xanthenediones constitute a key structural motif in a number of natural products,[12] and have been used as versatile synthons because of the inherent reactivity of the inbuilt pyran ring.[13] Synthesis of xanthenediones is a continuing hot topic because these moieties are privileged pharmacophores as well as valuable reactive intermediates for both synthetic and medicinal chemists.

Several elegant strategies for the synthesis of xanthenediones involving different types of catalysts have been reported.[1j,14–20] The above methods show varying degrees of successes as well as limitations, such as prolonged reaction times, low yields, use of toxic and costly reagents/catalysts, harsh reaction conditions, and complex work-up procedures. Keeping in view the disadvantages associated with reported protocols as well as increasing importance of xanthenediones in pharmaceutical and industrial chemistry, there still remains a high demand for the development of more general, efficient, and eco-friendly protocol to assemble such scaffolds. Indium trichloride has emerged as a highly efficient and effective potential Lewis acid catalyst imparting high regio- and chemo-selectivity in various chemical transformations,[21] due to its low toxicity, air and water compatibility, operational simplicity, and remarkable ability to suppress side reactions in acid sensitive substrates. A literature survey shows that P_2O_5 is a mild and

---

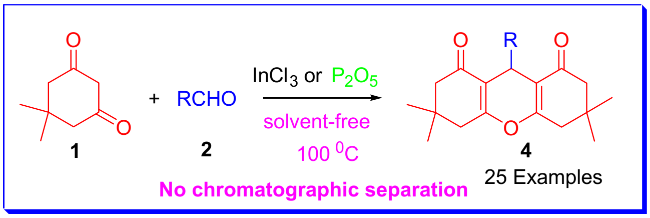
* Corresponding author. Fax: +91 542 2368127; e-mail address: mssinghbhu@yahoo.co.in (M.S. Singh).

0040-4020/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2011.03.078

selective catalyst, easy to handle and readily biodegradable, and has been utilized widely in various organic transformations,[22] and given many advantages in several organic synthesis.[23]

2. Results and discussion

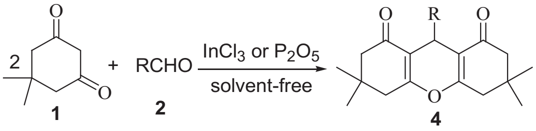
Our literature survey at this stage revealed that there are no reports on the use of $InCl_3$ or P_2O_5 as catalyst in the synthesis of octahydroxanthene-1,8-diones under solvent-free conditions. Our main strategy in this work is to develop a solvent-free organic reaction enhancement methodology, which is extremely fast and cleaner than conventional reactions, and lead to higher atom economy. In continuation of our interest in the area of clean synthesis under solvent-free conditions using $InCl_3$ or P_2O_5 as efficient and effective catalysts for the development of useful synthetic methodology[24] herein, we report a simple, efficient, and one-pot reaction of dimedone and aldehydes using $InCl_3$ or P_2O_5 at 100 °C for the preparation of 9-aryl/alkyl-3,3,6,6-tetramethyl-1,2,3,4,5,6,7,8-octahydroxanthene-1,8-diones in high yields (Scheme 1).



Scheme 1. $InCl_3$ and P_2O_5 promoted synthesis of 9-substituted tetramethyloctahydroxanthene-1,8-diones.

Initially, a blank reaction using 4-nitrobenzaldehyde and dimedone (mole rate 1:2) at 100 °C without $InCl_3$ or P_2O_5 was performed in order to establish the real effectiveness of the catalyst. We did not found the trace amount of desired product even after 12 h of heating. We then focused on optimizing the catalyst and its percentage loading. In order to evaluate the most appropriate catalyst loading, a model reaction using 4-nitrobenzaldehyde and dimedone (mole rate 1:2) was carried out using 5 mol %, 10 mol %, 15 mol %, and 20 mol % of $InCl_3$, and 10 mol %, 15 mol %, 20 mol %, and 25 mol % of P_2O_5 separately at different temperatures under solvent-free conditions (Table 1). It was found that 15 mol % of $InCl_3$ and 20 mol % of P_2O_5 showed maximum yield in minimum time at 100 °C (Table 1, entry 13). A further increasing of catalyst loading did not affect the yield (Table 1, entry 14). Herein, the reaction temperature was crucial in terms of the reaction rate and product yield. The above model reaction was carried out at different temperatures (60, 70, 80, and 100 °C) with 15 mol % of $InCl_3$ and 20 mol % of P_2O_5 loading separately. It was found that the desired compound **4b** was obtained in excellent yield at 100 °C (Table 1, entries 10–13). Further increase of the temperature (120 °C) neither increased the yield nor shortened the reaction time. The time taken for complete conversion (monitored by TLC) and the isolated yields at different temperatures are recorded in Table 1 for both the catalysts.

Table 1
Optimization of the catalyst on model reaction[a]



Entry	Temp (°C)	Method A ($InCl_3$) time/loading (%)/yield[b] (%)	Method B (P_2O_5) time/loading (%)/yield[b] (%)
1	100	12 h/no catalyst/0	12 h/no catalyst/0
2	60	2.0 h/5/87	2.5 h/10/90
3	70	1.5 h/5/90	2 h/10/88
4	80	80 min/5/92	1.5 h/10/89
5	100	70 min/5/94	80 min/10/92
6	60	1.5 h/10/88	1.75 h/15/87
7	70	75 min/10/87	1.5 h/15/85
8	80	60 min/10/91	70 min/15/90
9	100	40 min/10/93	45 min/15/92
10	60	75 min/15/82	85 min/20/82
11	70	60 min/15/90	65 min/20/84
12	80	30 min/15/92	40 min/20/91
13	100	15 min/15/98	20 min/20/96
14	100	20 min/20/98	23 min/25/96

[a] Reaction of 4-nitrobenzaldehyde (1 mmol) and dimedone (2 mmol) under solvent-free condition.
[b] Isolated pure yields.

With the optimized condition in hand, to explore the scope and generality of the reaction, we extended our study with other structurally varied aromatic, heteroaromatic, and aliphatic aldehydes to prepare a series of 9-aryl/heteroaryl/alkyl-3,3,6,6-tetramethyl-1,2,3,4,5,6,7,8-octahydroxanthene-1,8-diones (Table 2, entries 1–25). This protocol tolerates well aromatic aldehydes containing both electron-donating and electron-withdrawing substituents. The electronic effects and the nature of the substituents on the aldehydes show some obvious effects in terms of yields and reaction times. The aromatic aldehydes with electron-withdrawing groups as substrates reacted very well at faster rate and the reaction time is shorter compared with aromatic aldehydes with electron-donating groups. Though *meta*- and *para*-substituted aromatic aldehydes gave almost equally good results. However, *ortho*-substituted aromatic aldehydes turned out to be reluctant to undergo smooth reaction probably because of steric hindrance. Thus, longer reaction time is required for *ortho*-substituted aromatic aldehydes to get the corresponding products in high yields (Table 2, entries 3, 8, 12, and 17–22).

Table 2
Synthesis of tetramethyloctahydroxanthene-1,8-diones (**4a–y**)

Entry	R	Product	Time (min) $InCl_3/P_2O_5$	Yield[a] (%) $InCl_3/P_2O_5$
1	C_6H_5	**4a**	36/40	83/80
2	*p*-$NO_2\cdot C_6H_4$	**4b**	15/20	98/96
3	*o*-$NO_2\cdot C_6H_4$	**4c**	42/45	78/75
4	*m*-$NO_2\cdot C_6H_4$	**4d**	27/32	87/82
5	*p*-$Me\cdot C_6H_4$	**4e**	35/40	85/81
6	*p*-$Cl\cdot C_6H_4$	**4f**	45/48	83/79
7	*m*-$Cl\cdot C_6H_4$	**4g**	35/40	90/88
8	*o*-$Cl\cdot C_6H_4$	**4h**	60/63	80/76
9	*p*-$Br\cdot C_6H_4$	**4i**	55/58	82/79
10	*p*-$F\cdot C_6H_4$	**4j**	32/36	88/85
11	*p*-$OMe\cdot C_6H_4$	**4k**	42/47	83/81
12	*o*-$OMe\cdot C_6H_4$	**4l**	55/60	79/78
13	4-$Me_2N\cdot C_6H_4$	**4m**	50/55	74/72
14	2,4-$Cl_2\cdot C_6H_3$	**4n**	35/40	82/79
15	*p*-$OH\cdot C_6H_4$	**4o**	45/48	90/88
16	*m*-$OH\cdot C_6H_4$	**4p**	55/60	87/86
17	*o*-$OH\cdot C_6H_4$	**4q**	65/70	80/78
18	5-Br–2-$OH\cdot C_6H_3$	**4r**	60/65	83/80
19	5-NO_2–2-$OH\cdot C_6H_3$	**4s**	65/70	90/87
20	2-$OH\cdot C_{10}H_6$	**4t**	70/74	77/73
21	2-OH–3-$OEt\cdot C_6H_3$	**4u**	55/60	87/81
22	2-OH–3-$OMe\cdot C_6H_3$	**4v**	50/55	78/76
23	2-C_4H_3S	**4w**	25/30	70/68
24	$(CH_3)_2CH$	**4x**	65/70	60/58
25	$C_6H_5CH{=}CH$	**4y**	55/60	58/56

[a] Yields of isolated pure products.

In order to further investigate the scope of this reaction with aliphatic (isobutyraldehyde), heteroaromatic (thiophene-2-aldehyde), and α,β-unsaturated aldehyde (cinnamaldehyde) the reactions of dimedone were examined and found to produce the products in somewhat lower yields than those with aromatic aldehydes (Table 2, entries 23–25). However, furfuraldehyde under this protocol gave very poor yield of the expected product, which might be attributed toward the decomposition/polymerization of