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Introduction of two efficient catalysts for the synthesis of 1,8-dioxo-octahydroxanthene derivatives in the absence of solvent

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ABSTRACT

1,3-Dibromo-5,5-dimethylhydantoin (DBH) and benzyltriphenylphosphoniumtribromide (BTPTB) were used as efficient catalysts for the promotion of the synthesis of 1,8-dioxo-octahydroxanthene derivatives (DOXOs) *via* a one-pot three component condensation of aldehydes and cyclic 1,3-dicarbonyl compounds in the absence of solvent.

Keywords*: 1,8-Dioxo-octahydroxanthenes, Aldehydes, Cyclic 1,3-dicarbonyl compounds, 1,3-Dibromo-5,5-dimethylhydantoin, Benzyltriphenylphosphoniumtribromide, Solvent-free conditions.*

1. Introduction

Multi-component reactions (MCRs) are important class convergent organic reactions, in which three or more starting materials react to form a product that contains atoms derived from all participating reagents, often denoted as high atom economy. Due to this important ability, research of MCRs has naturally become a rapidly developing field in both academic and industrial research laboratories [1]. In addition, solvent-free conditions make synthesis simpler, save energy, and prevent solvent waste, hazards and toxicity [2-4]. It therefore remains a challenge to develop multi-component reactions with a suitable heterogeneous catalysts and the use of solvent-free conditions.

Xanthene and its derivatives are known as an important class of heterocyclic compounds widely used as leuco-dye, pH-sensitive fluorescent materials for visualization of biomolecules and utilized in laser technologies due to their photochemical and photo physical properties. They have been reported to possess diverse biological and therapeutic properties such as antibacterial, antiviral, anti-proliferative and anti-inflammatory activities [5-8].

There are several reports in the literature for the synthesis of 1,8-dioxo-octahydroxanthene derivatives employing aromatic aldehydes and cyclic 1,3-dicarbonyl compounds: these include $NaHSO_4.SiO_2$ or silica chloride [9], silica sulfuric acid [10], amberlyst-15 [11], Dowex-50W [12], trichloroisocyanuric acid (TCCA) [13], [Hmim]TFA [14], Brønsted acidic ionic liquids [15], I_2 [16], sulfonic acid functionalized imidazolium salts[17], $HClO_4$-SiO_2 and PPA-SiO_2 [18], and [bmim]HSO_4 [19]. Each of these methods have their own advantages but also some of them often 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, expensive reagents and hazardous reaction conditions. Therefore, it is important to find more convenient methods for the synthesis of these types of compounds.

2. Experimental

2.1. General

Chemicals were purchased from Fluka, Merck and Aldrich Chemical Companies. All yields refer to the isolated products. The purity determination of the substrate and reaction monitoring were accompanied by thin-layer chromatography (TLC) on silica-gel polygram SILG/UV 254 plates. The IR spectra were recorded on a Perkin Elmer 781 Spectrophotometer. In all cases the ^{1}H NMR spectra were recorded with BrukerAvance 400 MHz instrument. Chemical shifts are reported in parts per million in $CDCl_3$ with tetramethylsilane as an internal standard. ^{13}C NMR data were collected on BrukerAvance 100 MHz instrument.

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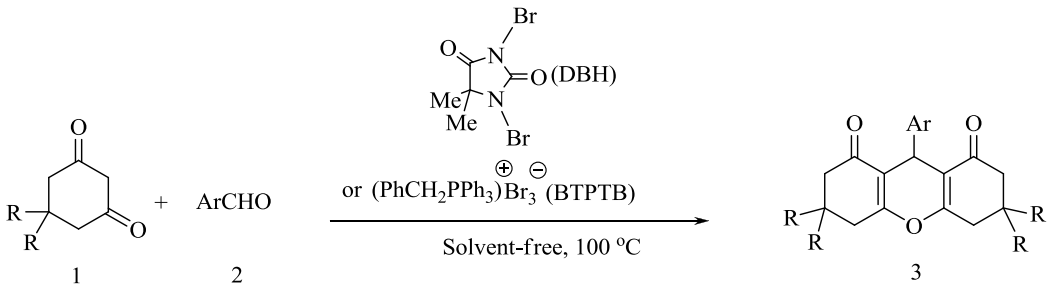

Fig. 1. Synthesis of 1,8-dioxo-octahydroxanthene derivatives.

2.2. General procedure for the synthesis of 1,8-dioxo-octahydroxanthene derivatives

A mixture of aldehyde (1.0 mmol), cyclic 1,3-dicarbonyl compound (2 mmol) and the catalyst (0.05 mmol) was heated in an oil bath (100°C). After completion of the reaction (monitored by TLC), the reaction was cooled to room temperature, ethanol (10 mL) was added and the mixture was filtered. Evaporation of the solvent, followed by recrystalization of the residue from EtOH affords the pure products in good to high yields. The physical and spectral data of the known compounds were in agreement with those reported in the literature. The spectral and analytical data for new compounds are as follow:

The selected spectral data

9-(3-Bromophenyl)-1,8-dioxo-octahydroxanthene (3):White solid, m.p. 279-281°C, IR (KBr, cm^{-1}): 3070, 2910, 2890, 1660, 1620, 1560, 1470, 1420, 1358, 1200, 1170, 1122, 957, 800, 680; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 1.95-2.1 (m, 4H), 2.30-2.44 (m, 4H), 2.55-2.63 (m, 2H), 2.66-2.73 (m, 2H), 4.79 (s, 1H), 7.11 (t, *J*=7.6 Hz, 1H), 7.26-7.36 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ: 20.3, 27.2, 31.6, 36.9, 116.3, 122.3, 127.7, 129.6, 131.0, 146.6, 164.3, 196.4.

9-(4-Cyanophenyl)-1,8-dioxo-octahydroxanthene(10):White solid, m.p. 270-273°C,IR (KBr, cm^{-1}): 3070, 2950, 2900, 2220, 1652, 1619, 1356, 1200, 1173, 1125, 958, 830, 610, 550; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 1.95-2.11 (m, 4H), 2.30-2.42 (m, 4H), 2.57-2.73 (m, 4H), 4.84 (s, 1H), 7.44 (d, *J*=8.0 Hz, 2H), 7.53 (d, *J*=8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ: 20.2, 27.1, 32.3, 36.8, 110.2, 115.8, 119.10, 129.4, 132.0, 149.7, 164.5, 196.5.

9-(3-Methoxyphenyl)-1,8-dioxo-octahydroxanthene (13):White solid, m.p. 192-194°C,IR (KBr, cm^{-1}): 3070, 2950, 1650, 1605, 1580, 1450, 1360, 1265, 1220, 1200, 1180, 1130, 1050, 960; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 1.99-2.1 (m, 4H), 2.3-2.45 (m, 4H), 2.54-2.71 (m, 4H), 3.81 (s, 3H), 4.83 (s, 1H), 6.69-6.71 (dd, J_1=8.0 Hz, J_2=1.6 Hz, 1H), 6.89-6.95 (m, 2H), 7.17 (t, *J*=8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ: 20.3, 27.2, 31.5, 37.0, 55.2, 111.5, 114.5, 116.8, 121.0, 129.0, 146.0, 159.4, 164.0, 196.5.

9-(2-Naphthyl)-1,8-dioxo-octahydroxanthene (14): White solid, m.p. 194-196 °C,IR (KBr, cm^{-1}): 3060, 2900, 2880, 1660, 1620, 1505, 1430, 1358, 1165, 1125, 1010, 955, 900, 853, 820, 745, 530; ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ:.1.9-2.05 (m, 4H), 2.26-2.39 (m, 4H), 2.55-2.63 (m, 2H), 2.67-2.74 (m, 2H), 5.03 (s, 1H), 7.29-7.45 (m, 2H), 7.53-7.56 (dd, J_1=9.6 Hz, J_2=1.6 Hz, 1H), 7.74-7.83 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ: 20.3, 27.2, 31.9, 37.0, 116.8, 125.4, 125.7, 127.0, 127.1, 127.5, 127.7, 128.0, 132.4, 133.4, 142.1, 164.2, 196.7.

Table 1. Effect of the solvent and the catalyst amount on the condensation of benzaldehyde and cyclohexanedione.

Solvent [a]	Amount of the catalyst (mmol)	DBH		BTPTB	
		Time (min)	Yield (%)	Time (min)	Yield (%)
n-Hexane	0.05	5	20	5	15
CH_2Cl_2	0.05	5	45	5	30
$CHCl_3$	0.05	5	30	5	30
CH_3CN	0.05	5	50	5	40
	0.05	5	80	5	72
	0.04	5	50	5	35
Solvent-free [b]	0.03	5	20	5	30
	0.02	5	20	5	25
	0.01	5	Trace	5	Trace

[a]Reaction was performed under reflux conditions.
[b]Reaction was performed at 100°C.

3. Results and Discussion

In recent years, use of bromo reagents in organic transformations, become an important part of our ongoing research program [20-24]. In continuation of these studies we have observed that cyclic 1,3-dicarbonyl compounds (1) can easily undergo the condensation with aromatic aldehydes (2) in the presence of 1,3-dibromo-5,5-dimethylhydantoin (DBH) or benzyltriphenyl phosphonium tribromide (BTPTB) to form 1,8-dioxo-octahydroxanthene derivatives (3) (Fig. 1). We first studied a reaction between 1,3-cyclohexanedione and benzaldehyde by screening the reaction conditions. In order to determine the optimum conditions, we examined the influence of the reaction temperature, the reaction time and the amounts of the catalysts. In all reactions the conditions were optimized for a 100% conversion. The best result was obtained by carrying out the reaction of benzaldehyde (1 mmol) and 1,3-cyclohexanedione (2 mmol) in the presence of 0.05 mmol of DBH or BTPTB at 100°C for 5 min in the absence of solvent (Table 1). After optimization of the reaction condition various aromatic aldehydes were subjected to reaction with 1,3-cyclohexanedione under the selected conditions. The results are summarized in Table 2. As indicated in this Table, in all cases the reaction gives the products in good to high yields and prevents problems which may associate with solvent use such as cost, handling, safety and pollution. To investigate the versatility of the selected method, the reaction of 5,5-dimethyl-1,3-cyclohexanedione with various aldehydes was also carried out in the presence of DBH or BTPTB under solvent free conditions at 100°C (Table 2**)**.

Table 2. Synthesis of 1,8-dioxo-octahydro-xanthenes derivatives.

Entry	Aldehydes	R	DBH Time(min)/ Yield (%)	BTPTB Time(min)/ Yield (%)	m.p. (°C)	
					Found[a,b]	Reported [Ref]
1	PhCHO	H	5/80	5/72	265-267	267-269 [25]
2	4-BrC_6H_4CHO	H	3/87	2/94	283-286	284-286 [25]
3	3-BrC_6H_4CHO	H	4/82	7/80	281-283	-
4	4-ClC_6H_4CHO	H	2/86	2/83	282-285	286-288 [25]
5	2-ClC_6H_4CHO	H	3/93	2/91	250-252	248-250 [25]
6	4-FC_6H_4CHO	H	3/88	2/91	275-276	275-277 [25]
7	4-$NO_2C_6H_4CHO$	H	1/93	2/87	255-256	263-265 [26]
8	3-$NO_2C_6H_4CHO$	H	3/89	3/87	281-282	286-288 [26]
9	2-$NO_2C_6H_4CHO$	H	6/90	8/82	238-240	245-246 [26]
10	4-CNC_6H_4CHO	H	2/90	3/83	273-275	-
11	4-MeC_6H_4CHO	H	4/87	2/93	255-258	262-263 [26]
12	4-$MeOC_6H_4CHO$	H	5/85	3/84	200-201	200-202 [25]
13	3-$MeOC_6H_4CHO$	H	5/80	5/76	192-194	-
14	2-Naphthaldehyde	H	5/81	5/77	197-198	-
15	PhCHO	Me	8/90	11/91	206-208	204-206 [19]
16	4-BrC_6H_4CHO	Me	7/92	7/92	233-235	240-242 [19]
17	4-ClC_6H_4CHO	Me	4/90	10/90	225-228	230-232 [19]
18	3-ClC_6H_4CHO	Me	5/90	8/91	185-187	182-184 [19]
19	4-FC_6H_4CHO	Me	5/90	5/90	226-227	224-226 [27]
20	4-$NO_2C_6H_4CHO$	Me	5/90	29/90	220-223	221-223 [19]
21	3-$NO_2C_6H_4CHO$	Me	5/90	10/91	170-171	170-172 [19]
22	4-MeC_6H_4CHO	Me	9/92	10/93	212-215	217-218 [19]
23	3-$MeOC_6H_4CHO$	Me	4/85	11/80	180-183	177-180 [13]
24	3,4-$(MeO)_2C_6H_3CHO$	Me	12/86	13/87	185-187	184-186 [28]
25	4-CNC_6H_4CHO	Me	7/90	13/91	220-222	230 [29]
26	C_6H_5CH=CHCHO	Me	11/91	12/92	172-174	174-176 [19]
27	1,4-$(CHO)_2C_6H_4$	Me	14/91	18/92	>300	>300 [19]

[a]Isolated yields.
[b]Products were confirmed by IR and NMR.

Table 3. Compared performance of various catalysts in the synthesis of 3,3,6,6-tetramethyl-9-(4-chlorophenyl)-1,8-dioxo-1,2,3,4,5,6,7-octahydro-xanthene (Table 1, entry 17).

Entry	Catalyst	Conditions	Time (h)	Yield (%)	Reference
1	DBH	Neat/100°C	4 / min	90	This work
2	BTPTB	Neat/100°C	10 / min	90	This work
3	$NaHSO_4.SiO_2$	CH_3CN/reflux	6.5	90	[9]
4	Silica sulfuric acid	Neat/80°C	1.5	94	[10]
5	Amberlyst-15	CH_3CN/reflux	5	94	[11]
6	Dowex-50	Neat/100°C	2.5	78	[12]
7	TCCA	EtOH/reflux	2.5	89	[13]
8	[Hmim]TFA	Neat/80°C	5	84	[14]
9	$[bmim]HSO_4$	Neat/80°C	3.5	95	[19]
10	DABCO-bromine	H_2O/reflux	2.5	80	[30]

It can be easily seen that in all cases, regardless of the nature of the substituents, the reaction gave the products in good to high yields during very short reaction times. Because of the formation of unidentified products the method is not useful for the synthesis of DOXOs from aliphatic aldehydes.

In order to show the merit of the proposed method, Table 3 compares the efficiency of DBH or BTPTB with other catalysts in the synthesis of 3,3,6,6-tetramethyl-9-(4-chlorophenyl)-1,8-dioxo- 1, 2, 3, 4, 5, 6, 7-octahydro-xanthene (Table 2, entry 17).

Although the actual role of DBH and BTPTB is not clear, the mechanism that is shown in Fig. 2 is selected as a most probable one.

4. Conclusion

In conclusion, in this study, we have developed an efficient method for the synthesis of 1,8-dioxo-octahydro-xanthene derivatives in the presence of 1,3-dibromo-5,5-dimethylhydantoin and benzyltriphenylphosphonium tribromide. Due to the relatively short reaction times, availability and low cost of the reagents, solvent-free reaction conditions, easy and clean work-up and good to high yields of the products, we believe it would be a useful addition to the available methodologies.

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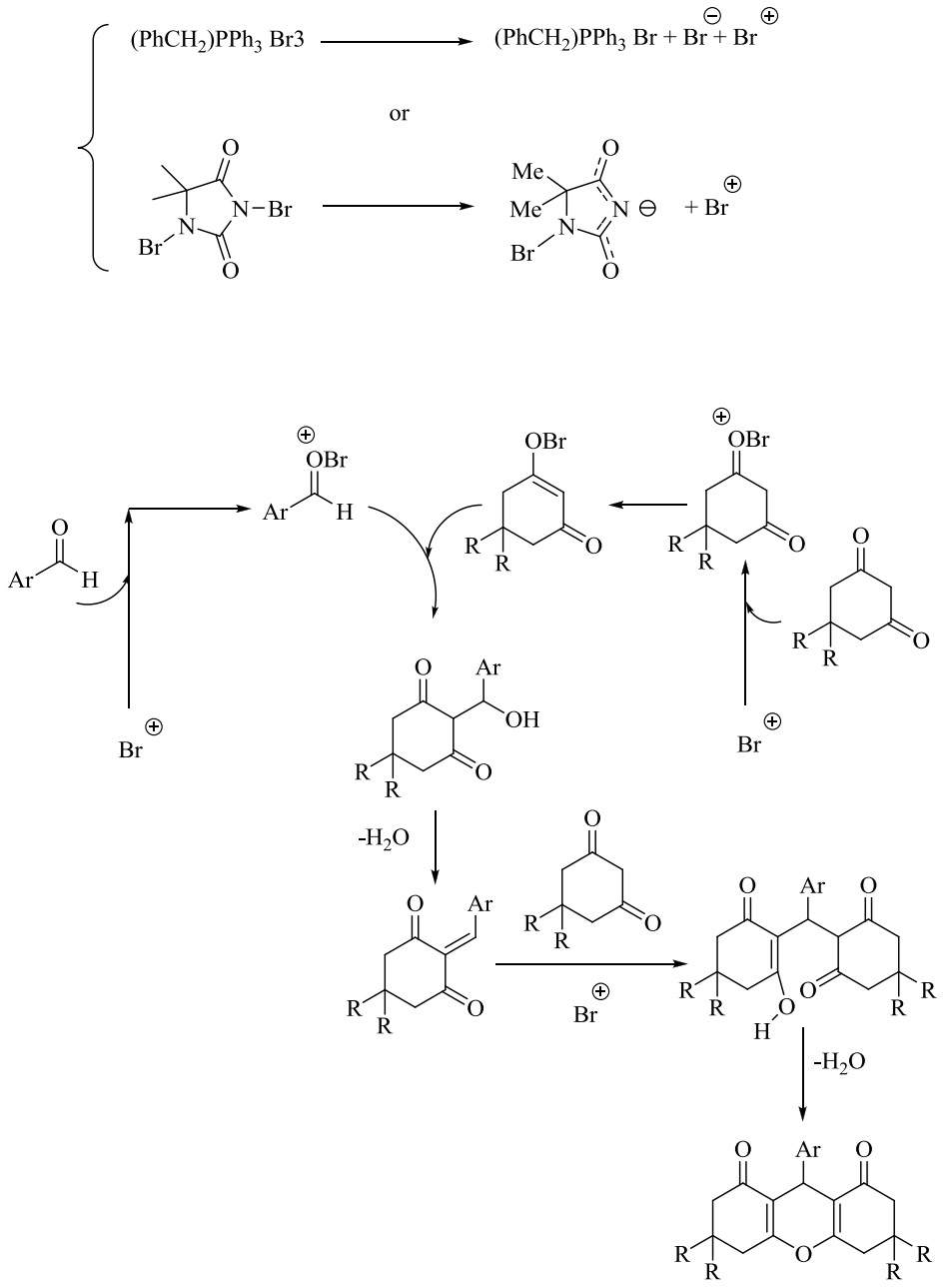

Fig. 2. Proposed mechanism of the reaction.

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