IRANIAN JOURNAL OF CATALYSIS

1,3-Dichloro-5,5-dimethylhydantoin: an efficient catalyst for the solvent free synthesis of 1,8-dioxo-octahydro-xanthenes

Farhad Shirini*, Kourosh Rad-Moghadam, Tahereh Naghdi

Department of Chemistry, College of Science, University of Guilan, Rasht, zip code 41335, I.R. Iran

Received 12 November 2011; received in revised form 15 March 2012; accepted 9 April 2012

ABSTRACT

This paper describes the applicability of 1,3-dichloro-5,5-dimethylhydantoin, as a cheap, stable and commercially available catalyst, in the promotion of the synthesis of 1,8-dioxo-octahydro-xanthenes (DOXOs) *via* the one-pot condensation of aldehydes and cyclic 1,3-dicarbonyl compounds. This novel synthetic method has the advantages of high yields, short reaction times, low cost and availability of the catalyst, solvent-free reaction conditions, simplicity and easy work-up compared to the conventional methods reported in the literature.

***Keywords**: Aldehydes, 1,8-Dioxo-octahydro-xanthenes, 1,3-Dichloro-5,5-dimethylhydantoin, Cyclic 1,3-dicarbonyl compounds, Solvent-free conditions.*

1. Introduction

Multi-component reactions (MCRs) are an important class of 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 wastes, hazards, and toxicity [2-4]. It therefore remains a challenge to develop multi-component reactions with a suitable heterogeneous catalysts and under of solvent-free conditions.

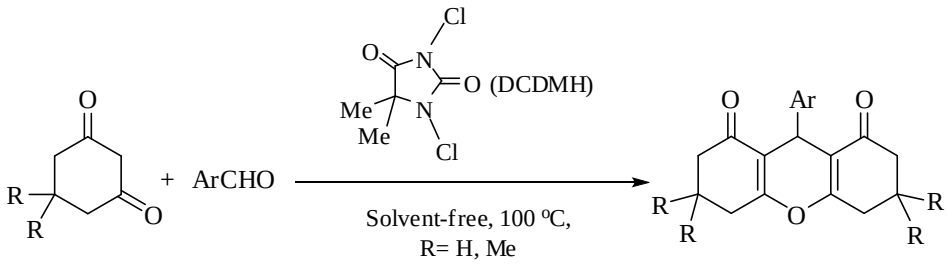
Xanthene and its derivatives are known as an important class of heterocyclic compounds widely used as leuco-dye, pH-sensitive fluorescent materials for visualization of biomolecules and utilized in laser technologies due to their photochemical and photophysical properties. They have been reported to 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-octahydro-xanthene 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-50 [12], trichloroisocyanuric acid (TCCA) [13], [Hmim]TFA [14], [Hbim]BF_4 [15], *p*-dodecylbenzenesulfonic acid [16], Fe^{3+}-montmorillonite [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 times, tedious work-up processes, low yield, lack of 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 type of compounds.

2. Experimental

2.1. General

Chemicals were purchased from Southern Clay Products, 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 (TL) on silica-gel polygram SILG / UV 254 plates. The IR spectra were recorded on a Perkin Elmer 781 Spectrophotometer. In all cases the ^1H NMR spectra were recorded with Bruker Avance 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 Bruker Avance 100 MHz instrument.

* Corresponding author: E-mail: shirini@guilan.ac.ir.
Tel./ Fax: +98 131 3226232.



Scheme 1.

2.2. General procedure

A mixture of an aromatic aldehyde (1 mmol), 5,5-dimethy-1,3-cyclohexanedione or 1,3-cyclohexanedione (2 mmol) and DCDMH (0.05 mmol) was heated in an oil bath (100 ^{O}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 recrystallization of the residue from

Table 1. Synthesis of 1,8-dioxo-octahydro-xanthenes.[a, b, c]

Entry	Aldehydes	R	Time (min) / Yield (%)	m.p. (^{o}C)	
				Found	Reported [Ref.]
1	PhCHO	H	8 / 80	265-267	267-269 [31]
2	4-BrC_6H_4CHO	H	5 / 87	283-286	284-286 [31]
3	3-BrC_6H_4CHO	H	6 / 83	279-281	-
4	4-ClC_6H_4CHO	H	4 / 84	282-285	286-288 [31]
5	2-ClC_6H_4CHO	H	5 / 92	250-251	248-250 [31]
6	4-FC_6H_4CHO	H	5 / 84	274-276	275-277 [31]
7	4-$NO_2C_6H_4$CHO	H	3 / 91	254-256	262-264 [31]
8	3-$NO_2C_6H_4$CHO	H	5 / 88	280-282	285-287 [31]
9	2-$NO_2C_6H_4$CHO	H	8 / 91	237-240	245-246 [34]
10	4-CNC_6H_4CHO	H	3 / 89	270-273	-
11	4-MeC_6H_4CHO	H	6 / 86	255-258	262-263 [34]
12	4-MeOC_6H_4CHO	H	7 / 83	200-201	200-202 [31]
13	3-MeOC_6H_4CHO	H	8 / 81	192-194	-
14	2-Naphthaldehyde	H	7 / 80	194-196	-
15	PhCHO	Me	11 / 91	206-208	200-202 [13]
16	4-BrC_6H_4CHO	Me	12 / 92	233-235	230-232 [13]
17	4-ClC_6H_4CHO	Me	8 / 90	225-228	230-232 [13]
18	3-ClC_6H_4CHO	Me	9 / 90	185-187	184-186 [19]
19	4-FC_6H_4CHO	Me	10 / 89	226-227	223-225 [32]
20	4-$NO_2C_6H_4$CHO	Me	10 / 91	228-230	225-227 [13]
21	3-$NO_2C_6H_4$CHO	Me	11 / 90	170-171	166-168 [13]
22	4-MeC_6H_4CHO	Me	14 / 91	212-215	216-218 [13]
23	3-MeOC_6H_4CHO	Me	9 / 80	181-183	177-180 [13]
24	3,4-$(MeO)_2C_6H_3$CHO	Me	16 / 87	185-187	184-186 [32]
25	4-CNC_6H_4CHO	Me	13 / 90	220-222	230 [32]
26	C_6H_5CH=CHCHO	Me	15 / 91	165-167	172-174 [13]

[a]Isolated yields.
[b]Products were confirmed by IR and NMR.
[c] Reaction conditions: Solvent-free, 100 ^{O}C.

EtOH afforded 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 (Table 1, entry 3): White solid, mp 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 (Table 1, entry 10): White solid, mp 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 (Table 1, entry 13): White solid, mp 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 (Table 1, entry 14): White solid, mp 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 (400 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.

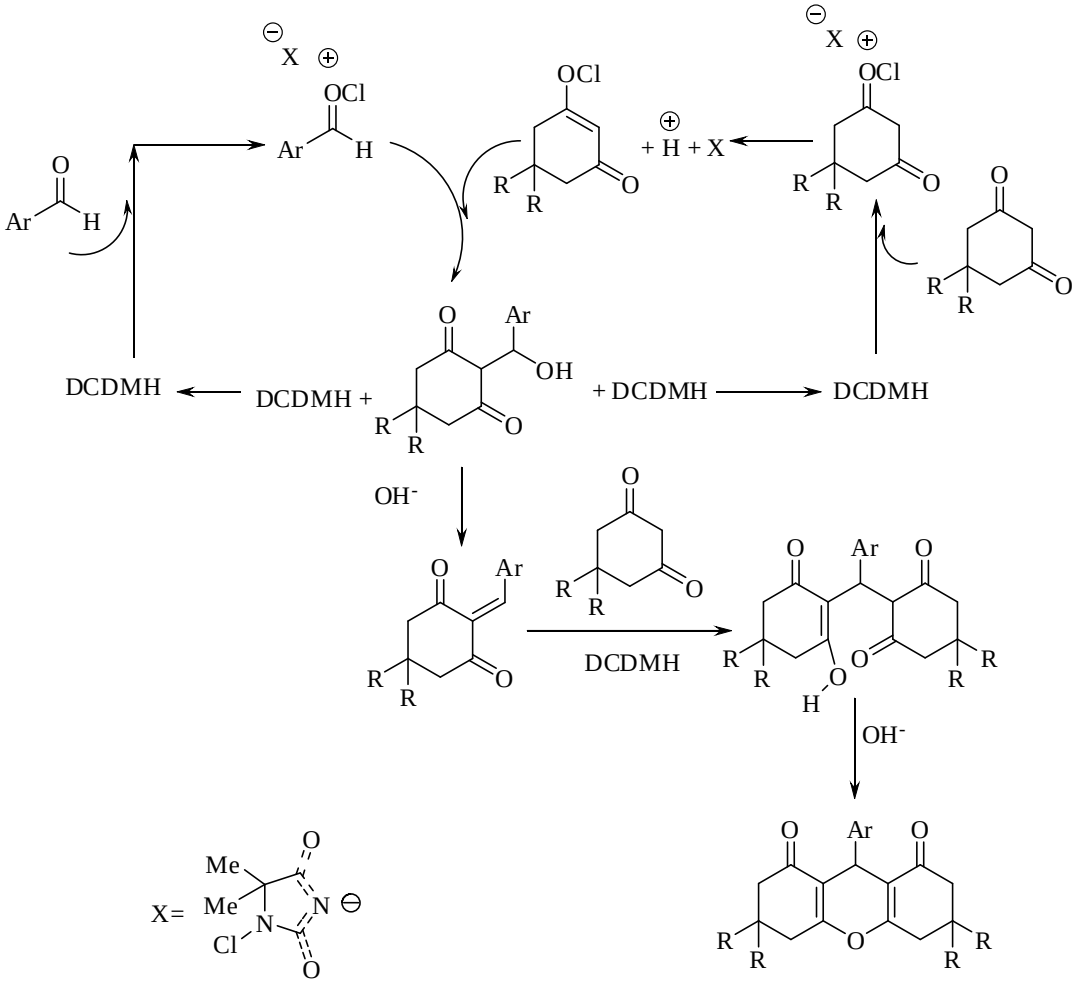
3. Results and Discussion

During the course of our studies on the application of *N*-haloamides in organic synthesis [20-22], we have found that 1,3-dichloro-5,5-dimethylhydantoin (DCDMH) is a cheap, stable and commercially available reagent. 1,3-Dichloro-5,5-dimethylhydantoin recently have been used as an efficient reagent for the α-chlorination of acetophenone [23], oxidative cleavage of oximes [24, 25], oxidation of urazoles [26], trimethylsilylation of alcohols [27], synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones [28], and Biginelli reaction [29]. Herein we wish to report the use of DCDMH in the efficient synthesis of 1,8-dioxo-octahydro-xanthenes under mild and solvent-free conditions (Scheme 1).

We first studied a reaction between 5,5-dimethyl-1,3-cyclohexanedione and benzaldehyde by screening the reaction conditions. In order to optimize the reaction conditions, we examined the influence of reaction temperature, the reaction time, and the amounts of the catalysts. In all reactions the conditions were optimized for 100% conversion. The best result was obtained by carrying out the reaction of benzaldehyde (1 mmol) and 5,5-dimethyl-1,3-cylohexanedione (2 mmol) in the presence of 0.05 mmol of DCDMH at 100 °C for 11 min in the absence of solvent (Table 1, entry 15). After optimization of the reaction conditions various aromatic aldehydes were subjected to reaction with 5,5-dimethyl-1,3-cylcohexanedione under the selected conditions (Table 1). As indicated in Table 1, 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 1,3-cyclohexanedione

Table 2. 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-octahydroxanthene (Table 1, entry 17).

Entry	Catalyst	Conditions	Time (h)	Yield (%)	Reference
1	DCDMH	Neat/100 °C	8/min	90	This work
2	$NaHSO_4.SiO_2$	CH_3CN/reflux	6.5	90	[9]
3	Silica sulfuric acid	Neat/80 °C	1.5	94	[10]
4	Amberlyst-15	CH_3CN/reflux	5	94	[11]
5	Dowex-50	Neat/100 °C	2.5	78	[12]
6	TCCA	EtOH/reflux	2.5	89	[13]
7	[Hmim]TFA	Neat/80 °C	5	84	[14]
8	[bmim]HSO_4	Neat/80 °C	3.5	95	[19]
9	DABCO-bromine	H_2O/reflux	2.5	80	[29]



Scheme 2. Proposed mechanism of the reaction.

was also carried out in the presence of DCDMH, with various aldehydes under solvent-free conditions at 100°C. The results are summarized in Table 1. It can be easily seen that in all cases, regardless of the nature of the substituent, 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 1,8-dioxo-octahydro-xanthenes from aliphatic aldehydes. In order to show the merit of the proposed method, Table 2 compares the efficiency of DCDMH 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 1, entry 17).

Although the actual role of DCDMH is not clear, on the basis of the obtained results and literature [28, 30], the mechanism that is shown in Scheme 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-xanthenes in the presence of 1,3-dichloro-5,5-dimethylhydantoin. Due to the short reaction times, availability and low cost of the reagent, 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.

Acknowledgments

We are thankful to the University of Guilan Research Council for the partial support of this work.

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