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A benign and efficient approach for one-pot, three-component synthesis of 2-hydroxy-12-aryl-8, 9, 10, 12-tetrahydrobenzo[a]xanthene-11-ones at ambient condition

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ABSTRACT

In the present research, acetic acid was applied as an eco-friendly catalyst and solvent for the synthesis of 2-hydroxy-12-aryl-8, 9, 10, 12-tetrahydrobenzo[a]xanthene-11-one derivatives by the one-pot, three-component coupling of aromatic aldehydes, 2,7-dihydroxynaphthalene and dimedone at room temperature. This procedure has some advantages, such as simplicity, high yield, cleaner reaction profiles, green and mild conditions, easy work-up, and no need to column chromatography.

Keywords: Acetic *acid, Tetrahydrobenzo[a]xanthenes, 2,7-dihydroxynaphthalene, Mild conditions*.

1. INTRODUCTION

Heterocyclic building blocks as the largest part of chemical entities play an elegant role in the design and synthesis of biologically active pharmaceuticals and chemicals [1]. The xanthenes and their derivatives are an important class of heterocyclic pharmaceutical compounds because of their significant and numerous spectrum of biological activities, such as antimicrobial [2], antiviral [3], antitumor [4], and anticancer [5] activities. Some of these compounds have applied in laser technology [6], fluorescent material for visualization of biomolecules [7], and also as dyes [8, 9].

Traditionally, the synthesis of heterocycles is carried out through multistep routes while MCRs approaches as a modern synthetic protocol making use of the flexible assembly of starting materials in situ. Simplicity, greater efficiency, atom economy, and preparation of molecular complexity with variety in one-pot conversions are some benefits of these reactions [10-12].

Owing to application of eco-friendly benign methods, multi-component reactions (MCRs) have been one of most important aspect of green chemistry. One approach to reduce the environmental impact of a reaction is diminished use of toxic solvents [13]. On the other hand, to obviate disadvantages of the solvent-free reactions, chemists have utilized available green solvents including water, polyethylene glycol, glycerol, lactic acid and acetic acid. In result, as one of the key green chemistry tools, application of green solvents has gained high priority [14].

Considering above facts and in continuum a part of our research programs to develop mild and greener methodologies [15-18], we have reported here the synthesis of 2-hydroxy-12-aryl-8, 9, 10, 12-tetrahydrobenzo[a]xanthene-11-one derivatives in one-pot synthesis by coupling of aromatic aldehydes, 2,7-dihydroxynaphthalene and dimedone in the presence of acetic acid as an efficient, non toxic, commercially available, high yielding, and inexpensive solvent in an environmentally benign condition.

Reported catalysts for the synthesis of 2-hydroxy-12-aryl-8,9,10,12-tetrahydrobenzo[a]xanthene- 11-one derivatives are including alum ($KAl(SO_4)_2.12H_2O$) [19], *p*-toluenesulfonic acid [20], Zr-MCM-41 [21], and lactic acid [22].

2. EXPERIMENTAL SECTION

2.1. General.

Melting points and IR spectra of all compounds were measured on an Electro thermal 9100 apparatus and FT-IR-JASCO-460 plus spectrometer. ^1H and ^{13}C NMR spectra of known compounds were recorded on a Bruker DRX-400 Avance instrument in $CDCl_3$ and DMSO at 300 and 400 MHz. All reagents were purchased from Merck (Darmastadt, Germany) and Fluka (Buchs, Switzerland) and used without further purification.

2.2. General procedure for preparation of 2-hydroxy-12-aryl-8, 9, 10, 12-tetrahydrobenzo[a]xanthene-11-ones.

A solution of aldehyde (1.0 mmol), 2,7-dihydroxynaphthalene (1.0 mmol) and dimedone (1.0 mmol) in acetic acid as catalyst and solvent stirred at room temperature for the time mentioned in Table 2. Thin layer chromatography (TLC) was applied for screening the evolution of the reaction. After completing the reaction, the solid product was filtrated and washed with acetic acid to separate the crude product. Then, the crude product was recrystallized from ethanol to afford the pure product.

2.3. Characterization data of selected compound.

12-(4-chlorophenyl)-2-hydroxy-9,9-dimethyl-8,9,10,12-tetrahydrobenzo[a]xanthen-11-one (**4c**): White powder; IR (KBr, cm^{-1}): 3200, 2955, 1627, 1590, 1448, 1379, 1232, 1164; ^1H NMR (400 MHz, $CDCl_3$): δ 0.88 (s, 3H, CH_3), 1.07 (s, 3H, CH_3), 2.14

(d, J = 16.0 Hz, 1H, CH_2), 2.35 (d, J = 16.0 Hz, 1H, CH_2), 2.57 (d, J = 18.0 Hz, 1H, CH_2), 2.69 (d, J = 20.0 Hz, 1H, CH_2), 5.36 (s, 1H, CH), 6.98-7.80 (m, 9H, Ar-H), 9.92 (s, 1H, OH).

2-Hydroxy-12-(2-Hydroxyphenyl)-9,9-dimethyl-8,9,10,12-tetrahydrobenzo[a]xanthen-11-one (**4i**). White powder; IR (KBr, cm^{-1}): 3235, 2952, 1621, 1588, 1450, 1389, 1232, 1177; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.05 (s, 3H, CH_3), 1.18 (s, 3H, CH_3), 2.36 (d, J = 16.5 Hz, 1H, CH_2), 2.44 (d, J = 16.5 Hz, 1H, CH_2), 2.62 (s , 2H, CH_2), 5.66 (s, 1H, CH), 6.57 (s, 1H, OH), 6.65-7.72 (m, 8H, Ar-H), 9.35 (s, 1H, OH).

2-Hydroxy-12-(2-Hydroxy-3-methoxylphenyl)-9,9-dimethyl-8,9,10,12-tetrahydrobenzo[a]xanthen-11-one (**4k**). White powder; IR (KBr, cm^{-1}): 3418, 3057, 2956, 1631, 1586, 1459, 1384, 1252, 1231, 1176; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.02 (s, 3H, CH_3), 1.17 (s, 3H, CH_3), 2.34 (d, J = 16.5 Hz, 1H, CH_2), 2.43 (d, J = 16.8 Hz, 1H, CH_2), 2.62 (s , 2H, CH_2), 3.88 (s, 3H, OCH_3), 5.66 (s, 1H, CH), 6.34-7.71 (m, 8H, Ar-H), 8.96 (s, 1H, OH).

2-Hydroxy-9,9-dimethyl-12-(3,4-dimethoxylphenyl)-8,9,10,12-tetrahydrobenzo[a]xanthen-11-one (**4m**). White powder; IR (KBr, cm^{-1}): 3184, 2954, 1627, 1595, 1444, 1381, 1223, 1137; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.04 (s, 3H, CH_3), 1.17 (s, 3H, CH_3), 2.37 (d, J = 17.1 Hz, 1H, CH_2), 2.44 (d, J = 16.5 Hz, 1H, CH_2), 2.64 (s , 2H, CH_2), 3.64 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3), 5.80 (s, 1H, CH), 6.60-7.76 (m, 8H, Ar-H), 6.68 (s, 1H, OH), 8.24 (s, 1H, OH).

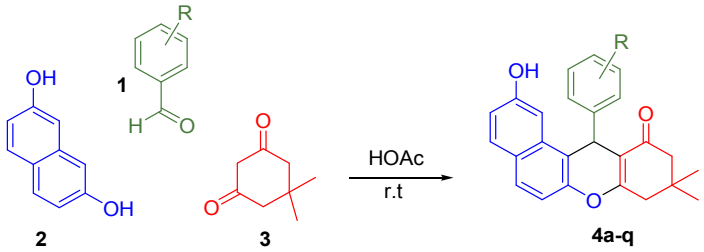
2-Hydroxy-9,9-dimethyl-12-(4-methylphenyl)-8,9,10,12-tetrahydrobenzo[a]xanthen-11-one (**4o**). White powder; IR (KBr, cm^{-1}): 3183, 2958, 1631, 1590, 1449, 1379, 1232, 1139; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.05 (s, 3H, CH_3), 1.18 (s, 3H, CH_3), 2.18 (s, 3H, CH_3), 2.36 (d, J = 16.5 Hz , 1H, CH_2), 2.45 (d, J = 16.5 Hz , 1H, CH_2), 2.66 (s , 2H, CH_2), 5.86 (s, 1H, CH), 6.93-7.83 (m, 9H, Ar-H), 8.70 (s, 1H, OH).

2-Hydroxy-12-(3-hydroxyphenyl)-9,9-dimethyl-8,9,10,12-tetrahydrobenzo[a]xanthen-11-one (**4r**). White powder; IR (KBr, cm^{-1}): 3331, 3107, 2956, 1619, 1590, 1446, 1384, 1229, 1136; ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.94 (s, 3H, CH_3), 1.14 (s, 3H, CH_3), 2.20 (s, 1H, CH_2), 2.34 (s, 2H, CH_2), 2.52 (s, 1H, CH_2), 6.23 (s, 1H, CH), 6.58-7.77 (m, 9H, Ar-H), 9.05 (s, 1H, OH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.7, 29.3, 32.3, 34.3, 50.6, 105.7, 113.7, 113.8, 114.0, 115.5, 116.0, 117.6, 119.3, 125.9, 129.1, 129.3, 130.6, 133.0, 146.5, 148.2, 156.8, 157.5, 164.3, 196.3. MS m/z (%): 152.1(12), 237.1 (12), 293.1 (100), 386.2(M+, 20).

2-Hydroxy-9,9-dimethyl-12-(3-methylphenyl)-8,9,10,12-tetrahydrobenzo[a]xanthen-11-one (**4s**). White powder; IR (KBr, cm^{-1}): 3169, 2955, 1621, 1597, 1472, 1383, 1229, 1146; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.07 (s, 3H, CH_3), 1.19 (s, 3H, CH_3), 2.11 (s, 3H, CH_3), 2.39 (d, J = 16.4 Hz , 1H, CH_2), 2.45 (d, J = 16.4 Hz , 1H, CH_2), 2.68 (s , 2H, CH_2), 5.94 (s, 1H, CH), 6.83-7.94 (m, 9H, Ar-H), 9.05 (s, 1H, OH). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 21.3, 27.3, 29.0, 32.6, 41.5, 50.5, 106.2, 113.8, 114.3, 116.2, 117.1, 125.6, 126.4, 126.8, 127.1, 128.1, 129.7, 130.2, 133.1, 137.5, 144.4, 147.8, 156.1, 165.7, 199.2. MS m/z (%): 237.1 (11), 293.2(100), 294.2 (26), 384.3 (M+, 27).

3. RESULTS SECTION

Initially, to afford appropriate conditions for the synthesis of 2-hydroxy-12-aryl-8,9,10,12-tetrahydrobenzo[a]xanthene- 11-ones , we accomplished the one-pot, three-component reaction of 4-chlorobenzaldehyde (1.0 mmol), 2,7-dihydroxynaphthalene (1.0 mmol), and dimedone (1.0 mmol) as a model reaction in various solvents (1mL) in the presence of acetic acid as catalyst at room temperature. The results are indicated in Table 1. Different solvents in the presence of acetic acid as an inexpensive, green and available catalyst were utilized in the model reaction. As can be seen from Table 1, acetic acid is our choice as solvent and catalyst for the reaction, and the desired product was gained in excellent yield and high purity (Table 1, entry 6). While under solvent-free and catalyst-free conditions, the reaction did not progress even after 24 h (Table 1, entry 1).



Scheme 1. Acetic acid catalyzed one-pot synthesis of 2-hydroxy-12-aryl-8,9,10,12-tetrahydrobenzo[a]xanthene-11-ones.

Table 1. Different Solvents effect on the reaction between 4-chlorobenzaldehyde, 2,7-dihydroxynaphthalene and dimedone with 20 mol% of catalyst in at room temperature

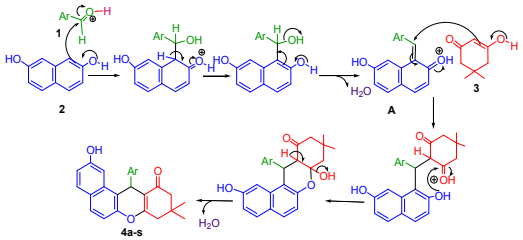
Entry	Catalyst	Solvent	Time (h)	Yield (%)
1	-	-	24	-
2	AcOH	EtOH	24	-
3	AcOH	H_2O	24	-
4	AcOH	CH_3CN	24	-
5	AcOH	CH_2Cl_2	24	-
6	AcOH	AcOH	35(min)	94

To evaluate the range and feasibility of this multi-component reaction, a series of 2-hydroxy-12-aryl-8, 9, 10, 12-tetrahydrobenzo[a]xanthene-11-one derivatives were synthesized under the optimum reaction conditions. The results in Table 2 illustrated that the strategy could be exerted to aromatic aldehydes either with electron-withdrawing groups or electron-donating groups with satisfied yields (from 80% to 95%). It is notable that the electronic nature of substituents of the aromatic aldehyde has no obvious effect on the multi-component reaction.

Table 2. One-pot, three-component synthesis of 2-hydroxy-12-aryl-8, 9, 10, 12-tetrahydrobenzo[a]xanthene-11-ones in the presence of acetic acid at room temperature

Entry	R	Product	Time (min)	Yield (%)	Mp (°C)	
					Found	Reported[Ref]
1	H	**4a**	57	80	263-267	>300[20]
2	2-Cl	**4b**	50	83	277-280	280-282[21]
3	4-Cl	**4c**	35	94	304-306	>300[19]
4	4-F	**4d**	46	89	284-287	278-280[19]
5	3-Br	**4e**	45	83	311-318	>300 [20]
6	4-Br	**4f**	46	91	305-307	303-305[20]
7	3-NO_2	**4g**	45	87	308-311	>300[20]
8	4-NO_2	**4h**	43	88	297-299	288-290[19]
9	2-OH	**4i**	125	82	277-279	276-278[21]
10	2-OH, 5-Br	**4j**	90	88	298-301	308-310[21]
11	2-OH, 3-OMe	**4k**	125	83	278-281	269-270[21]
12	4-OMe	**4l**	30	90	277-280	282-284[19]
13	3,4- di OMe	**4m**	100	82	247-250	256-258[20]
14	2-Me	**4n**	65	81	290-293	288-291[22]
15	4-Me	**4o**	40	84	298-300	298-300[21]
16	1-Naphthyl	**4p**	130	95	301-304	>300[20]
17	2-Naphthyl	**4q**	105	90	300-304	272-274[20]
18	3-OH	**4r**	60	91	296-298	This work
19	3-Me	**4s**	50	90	274-277	This work

In a plausible mechanism, at first, aldehyde is activated by the proton from acetic acid to decrease the energy of the transition state. Next, *o*-quinone methides (*o*-QMs) intermediate **A** [23] is formed by the nucleophilic attack of 2,7-dihydroxynaphthalene **2** to the carbonyl group of the activated aldehyde **1**. In the next stage, with a Michael addition of dimedone **3** to o-QMs activated by acetic acid and remove one molecule of H_2O to obtain 2-hydroxy-12-aryl-8,9,10,12-tetrahydrobenzo[a]xanthene-11-ones (**4a-4s**). To illustrate the notable benefits our work, the results afforded by the reaction between 4-chlorobenzaldehyde, 2,7-dihydroxynaphthalene and dimedone compared with other results reported in the literature, (Table 4). According to the sixth principle of the twelve principles of green chemistry, minimum amount of energy should be used for their environmental and economic impacts, so synthetic methods should be occurred under ambient conditions [24]. This methodology was performed at room temperature in terms of economic and environmental approach. Also, acetic acid has applied as an efficient, non toxic, inexpensive, and commercially available catalyst, and solvent.



Scheme 2. The proposed mechanism for the synthesis of 2-hydroxy-12-aryl-8, 9, 10, 12 -tetrahydrobenzo[a] xanthene-11-ones using acetic acid.

Table 4. Comparison of the results afforded from the synthesis of 2-hydroxy-12-aryl-8, 9, 10, 12 -tetrahydrobenzo[a]xanthene-11-ones with using the reaction between 4-chlorobenzaldehyde, 2,7-dihydroxynaphthalene and dimedone in the presence of acetic acid with those obtained via other catalysts.

Entry	Catalyst	Time (min)	Reaction conditions	Yield (%)	Reported[Ref]
1	$KAl(SO_4)_2.12H_2O$	45	PEG-400, 80 °C	86	19
2	*p*-TSA	2.5h	Reflux in EtOH	94	20
3	*p*-TSA	2h	[bmim]BF_4, 50°C	94	20
4	Zr-MCM-41	10	80 °C/ Solvent-free	88	21
5	Lactic acid	5	50 °C/Solvent free	95	22
6	Acetic acid	35	r.t.	94	This work

4. CONCLUSIONS

Conclusion part of the manuscript clearly says that the reaction has carried out under eco-friendly condition. We have developed a simple and highly effective one-pot synthesis of 2-hydroxy-12-aryl-8, 9, 10, 12-tetrahydrobenzo[a]xanthene-11-ones

at ambient temperature. The reaction proceeds in the presence of acetic acid as catalyst and solvent with advantages including of benign environmentally and commercially available. The simple workup procedures, mild condition, clean reaction conditions, and the minimum pollution of the environment make this protocol economically attractive.

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6. ACKNOWLEDGEMENTS

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