

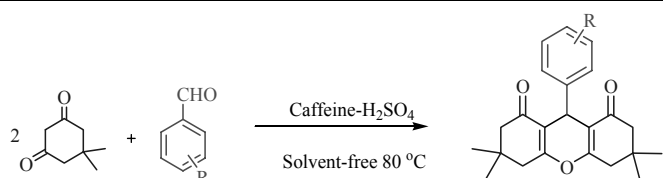
CAFFEINE-H₂SO₄: AN EFFICIENT BIO-BASED CATALYST FOR THE ONE-POT PREPARATION OF 1,8-DIOXO-OCTAHYDRO-XANTHENES

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Caffeine-H₂SO₄ has been utilized as an efficient acidic catalyst in the one-pot preparation of 1,8-dioxo-octahydro-xanthenes. Application of Caffeine-H₂SO₄ has some advantages including short reaction time, high yield of the products and recyclability of the catalyst.



INTRODUCTION

Multi-component reactions (MCRs) have interested organic chemists due to their simplicity, high yield of the products, one-pot synthesis and eco-friendly reaction conditions.¹ Because of the great potential of MCRs in designing novel organic reactions, different strategies have been devised, including solvent-free conditions, application of homogeneous or heterogeneous catalysts, or performing reaction in unconventional solvents.²

Solvent-free organic reactions have attracted much interest particularly from the viewpoint of green chemistry.³ The possibility of performing condensation reactions under solvent-free conditions with a heterogeneous catalyst could enhance their efficiency from an economic as well as ecological point of view.^{4,5} The eco-friendly, solvent-free approach opens up numerous possibilities for conducting rapid organic synthesis and functional group transformations more efficiently.⁶

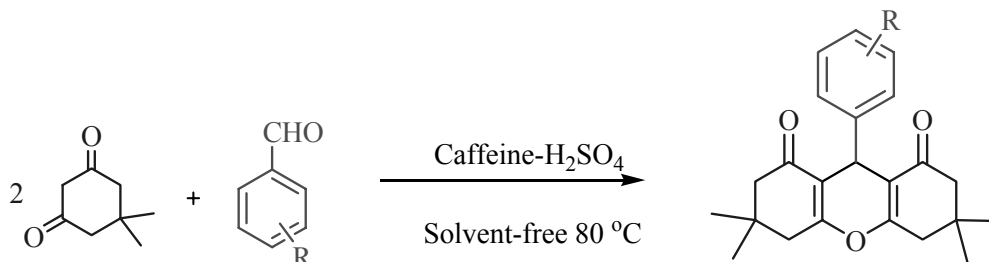
According to the biological properties of xanthene derivatives, these compounds occupy a prominent position in medicinal chemistry⁷ due to their bactericidal,⁸ anti-inflammatory⁹ and antiviral

activity.¹⁰ It is worth mentioning that, a number of natural products have xanthene unit in their structure.¹¹ Thus the synthesis of xanthenes is of great importance in organic synthesis.

1,8-dioxo-octahydro-xanthenes, have been prepared through the dehydration of dimedone and aromatic aldehydes, in the presence of a catalyst, such as, tetrabutylammonium hydrogen sulfate¹² Sc³⁺-montmorillonite,¹³ HClO₄.SiO₂ and PPA-SiO₂,¹⁴ PMA-SiO₂,¹⁵ acidic ionic liquids,¹⁶ HPWA/MCM-41 mesoporous molecular sieves,¹⁷ silica-supported preyssler nano particles,¹⁸ MCM-41-R-SO₃H,¹⁹ acid functionalized SBA-15 and MCM-41,²⁰ and Silica bonded *N*-propyl sulfamic acid.²¹ However some of these methods suffer from long reaction time, low yield of the products or expensive catalyst. Thus search for green methods with recyclable catalysts are in still needed.

In continuation of our previous works on the applications of reusable acid catalysts in organic synthesis,^{22,23} we decided to investigate the synthesis of 1,8-dioxo-octahydro-xanthenes in the presence of catalytic amounts of Caffeine-H₂SO₄ under solvent-free conditions (Scheme 1).

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Scheme 1 – One-pot preparation of 1,8-dioxo-octahydro-xanthenes.

EXPERIMENTAL

General

All commercially available chemicals were purchased from commercial companies and used without further purification. Products were characterized by their physical constant and comparison with authentic samples. Reaction monitoring was accomplished by TLC on silica gel polygram SILG/UV 254 plates. The IR spectra were recorded on a BOMEM MB-Series 1998 FT-IR spectrophotometer using KBr pellets for the samples and the catalyst in the range of 4000–400 cm^{-1} . ^1H and ^{13}C NMR spectra were recorded in CDCl_3 and $\text{DMSO-}d_6$ on a Bruker Advanced DPX 400 MHz spectrometer using TMS as internal standard. Caffeine- H_2SO_4 was prepared according to our previous report.²³

Typical procedure for the preparation of 1,8-dioxo-octahydro-xanthenes

A mixture of, aromatic aldehyde (1.0 mmol), dimesone (2.0 mmol), and Caffeine- H_2SO_4 (0.025 g, 10 mol%) were mixed for 25-45 minutes under solvent-free conditions at 80 °C. Completion of the reaction was indicated by TLC [TLC acetone/n-hexane (3:10)]. After completion of the reaction, the mixture was washed with water and the crude product was recrystallized in hot ethanol to afford the pure product.

3,3,6,6-Tetramethyl-9-(phenyl)-1,8-dioxo-octahydroxanthene (Table 2, Entry 1):

White powder, ^1H NMR (400 MHz, $\text{DMSO-}d_6$): δ (ppm) 7.21 (t, $J = 7.20$ Hz, 2H), 7.18 (d, $J = 7.0$ Hz, 2H), 7.10 (t, $J = 7.0$ Hz, 1H), 2.58 (d, $J = 17.7$ Hz, 2H), 4.53 (s, 1H), 2.53 (d, $J = 17.1$ Hz, 2H), 2.27 (d, $J = 16.2$ Hz, 2H), 2.09 (d, $J = 16.1$ Hz, 2H), 1.04 (s, 6H), 0.90 (s, 6H).¹²

3,3,6,6-Tetramethyl-9-(4-nitrophenyl)-1,8-dioxo-octahydroxanthene (Table 2, Entry 2):

White powder, ^1H NMR (400 MHz, CDCl_3): δ (ppm) 8.08 (2H, $J = 8.2$ Hz, 2H), 7.48 (d, $J = 8.2$ Hz, 2H), 4.83 (s, 1H), 2.51 (t, $J = 18.7$ Hz, 4H), 2.26 (d, $J = 16.3$ Hz, 2H), 2.16 (d, $J = 16.3$ Hz, 2H), 1.12 (s, 6H), 0.99 (s, 6H).¹²

3,3,6,6-Tetramethyl-9-(3-nitrophenyl)-1,8-dioxo-octahydroxanthene (Table 2, Entry 3):

White powder, ^1H NMR (400 MHz, CDCl_3): δ (ppm) 8.06 (s, 1H), 7.99 (d, $J = 8.2$ Hz, 1H), 7.81 (d, $J = 7.5$ Hz, 1H), 7.41 (t, $J = 7.9$ Hz, 1H), 4.85 (s, 1H), 2.53 (t, $J = 18.5$ Hz, 4H), 2.27 (d, $J = 16.3$ Hz, 2H), 2.18 (d, $J = 16.3$ Hz, 2H), 1.13 (s, 6H), 1.01 (s, 6H).¹²

3,3,6,6-Tetramethyl-9-(4-hydroxyphenyl)-1,8-dioxo-octahydroxanthene (Table 2, Entry 4):

White powder, ^1H NMR (400MHz, $\text{DMSO-}d_6$) δ (ppm) 7.06-7.08 (2H, d, $J = 8.0$ Hz, ArH), 6.71 (1H, s, OH), 6.53-6.55 (2H, d, $J = 8.0$ Hz, ArH), 4.62 (1H, s, H-9), 2.47 (4H, s,

$2 \times \text{CH}_2$, H-2, H-7), 2.30 (4H, dd, $J = 1.6$ Hz, $J = 4.0$ Hz, $2 \times \text{CH}_2$, H-4, H-5), 1.10 (6H, s, $2 \times \text{CH}_3$), 0.99 (6H, s, $2 \times \text{CH}_3$).¹²

3,3,6,6-Tetramethyl-9-(4-methylphenyl)-1,8-dioxo-octahydroxanthene (Table 2, Entry 5):

White powder, ^1H NMR (400 MHz, CDCl_3): δ (ppm) 7.20 (d, $J = 6.9$ Hz, 2H), 7.04 (d, $J = 7.5$ Hz, 2H), 4.74 (s, 1H), 2.49 (s, 4H), 2.17–2.27 (m, 7H), 1.25 (s, 6H), 1.02 (s, 6H).¹²

3,3,6,6-Tetramethyl-9-(4-methoxyphenyl)-1,8-dioxo-octahydroxanthene (Table 2, Entry 6):

White powder, ^1H NMR (400 MHz, CDCl_3): δ (ppm) 7.22 (d, $J = 8.8$ Hz, 2H), 6.77 (d, $J = 8.8$ Hz, 2H), 4.72 (s, 1H), 3.75 (s, 3H), 2.48 (s, 4H), 2.25 (d, $J = 16.4$ Hz, 2H), 2.18 (d, $J = 16.4$ Hz, 2H), 1.12 (s, 6H), 1.01 (s, 6H).¹²

3,3,6,6-Tetramethyl-9-(2-chloroxyphenyl)-1,8-dioxo-octahydroxanthene (Table 2, Entry 7):

White powder, ^1H NMR (CDCl_3 , 400 MHz): δ (ppm) 7.09-7.46 (4H, m, ArH), 5.03 (s, 1H), 2.48 (s, 4H), 2.26 (d, 2H, $J = 16.2$ Hz), 2.19 (d, 2H, $J = 16.2$ Hz), 1.13 (s, 6H), 1.05 (s, 6H).¹²

3,3,6,6-Tetramethyl-9-(4-cyanophenyl)-1,8-dioxo-octahydroxanthene (Table 2, Entry 8):

White powder, IR (KBr, cm^{-1}) 3014, 2985, 2224, 1663, 1500, 1471; ^1H NMR (400MHz, CDCl_3) δ (ppm) 7.4, 7.51 (4H, dd, $J = 4.9$ Hz, ArH), 4.76(1H, s), 2.49(4H, t, $2 \times \text{CH}_2$), 2.13-2.26 (4H, dd, $J = 19.6$ Hz, $2 \times \text{CH}_2$), 1.11 (6H, s, $2 \times \text{CH}_3$), 0.98 (6H, s, $2 \times \text{CH}_3$); ^{13}C NMR (100MHz, CDCl_3) δ (ppm) 196.3, 162.9, 149.5, 131.9, 129.3, 119.0, 114.5, 110.1, 50.6, 40.7, 32.4, 32.2, 29.2, 27.2.²⁴

RESULTS AND DISCUSSION

Caffeine- H_2SO_4 was easily prepared by addition of conc. H_2SO_4 to a solution of caffeine in CH_2Cl_2 and subsequent stirring for 24 h.²³ Caffeine- H_2SO_4 is now introduced as an efficient acidic catalyst for the preparation of 1,8-dioxo-octahydro-xanthenes.

We have recently characterized this catalyst by FT-IR, ^1H NMR, ^{13}C NMR and TGA.²³ A model reaction of benzaldehyde (1.0 mmol), dimesone (2.0 mmol) with different Caffeine- H_2SO_4 loadings were conducted in different temperatures under solvent-free conditions (Table 1). The best results were obtained at 80 °C with 10 mol% catalyst loading. Higher percentage of catalyst loading (15 mol%) neither increases the yield nor lowers the conversion time (Table 1).

Table 1

Optimum reaction conditions for the reaction of Dimedone (2 mmol) and benzaldehyde (1 mmol)

Entry	Solvent and/or Condition	Catalyst mol%	T (°C)	Time (min)	Yield (%)
1	solvent-free	5	25	60	15
2	“	5	50	60	45
3	“	-	80	60	-
4	“	5	80	120	62
5	“	10	80	25	96
6	“	15	80	30	92

Table 2

One-pot preparation of 1,8-dioxo-octahydro-xanthenes in the presence of Caffeine-H₂SO₄ under solvent-free conditions at 80 °C

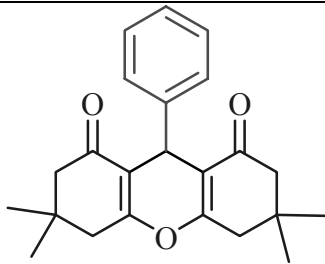
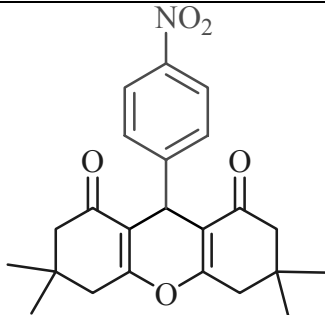
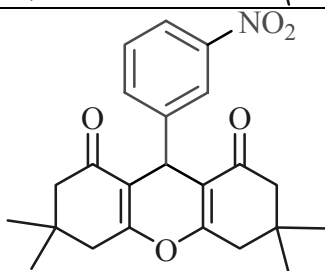
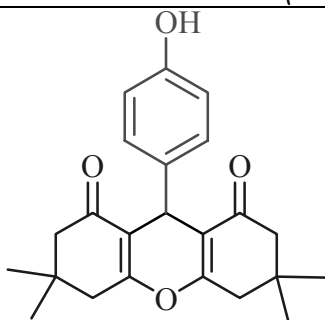
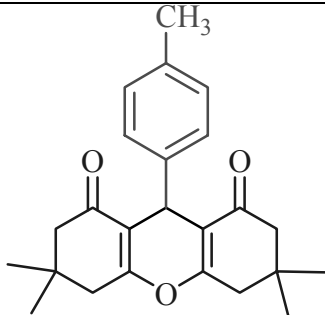
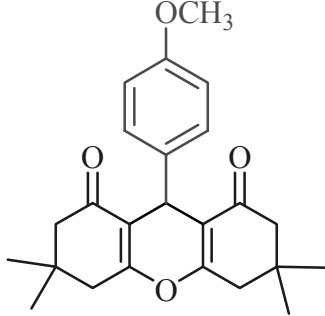
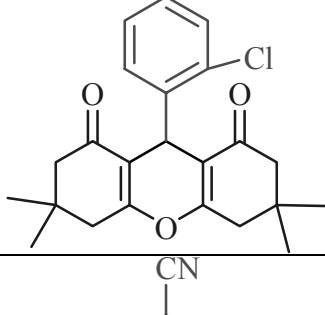
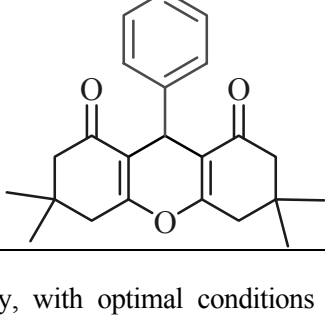
Entry	Product	Time (min)	Yield (%)	Melting point, °C	
				Found	Reported
1		25	96	205-207	204-206 ¹²
2		30	97	222-224	221-223 ¹²
3		30	90	174-175	170-172 ¹²
4		30	89	246-248	246-247 ¹²

Table 2 (continued)

5		35	91	218-219	217-218 ¹²
6		45	87	243-245	240-242 ¹²
7		30	92	226-227	225-227 ¹²
8		25	94	216-218	217-218 ²⁴

Subsequently, with optimal conditions in hand, 1:2 molar ratios of aldehyde and dimedone and 10 mol% of Caffeine-H₂SO₄ at 80 °C under solvent-free conditions, a series of 1,8-dioxo-octahydro-xanthenes were prepared (Table 2). Gratifyingly, a wide range of aromatic aldehydes were well tolerated under the optimized reaction conditions. The time taken for complete conversion (monitored by TLC) and the isolated yields are recorded in Table 2. All compounds were characterized by their satisfactory spectral studies, and compared with authentic ones.

Owing to the increasing interest in environmental protection, and the concept of green chemistry, the recyclability and reusability of the catalyst was performed. After completion of the reaction, chloroform (2 mL) was added and the catalyst was

centrifuged. The separated catalyst was dried and reused for four subsequent cycles. Surprisingly consistent performance of the catalyst was observed in all the cycles (Fig 4).

To compare our proposed method with state of the art, the reaction of dimedone and *p*-nitrobenzaldehyde was considered as a representative example (Table 3). While in most of these cases (except entry 2) comparative yields of the desired product were obtained following the Caffeine-H₂SO₄-catalyzed procedure, the reported procedures required long reaction time (entry 1, 3, 4), or high catalyst loading (entry 4, 5). These results clearly demonstrate that Caffeine-H₂SO₄ is an equally or more efficient catalyst for this reaction.

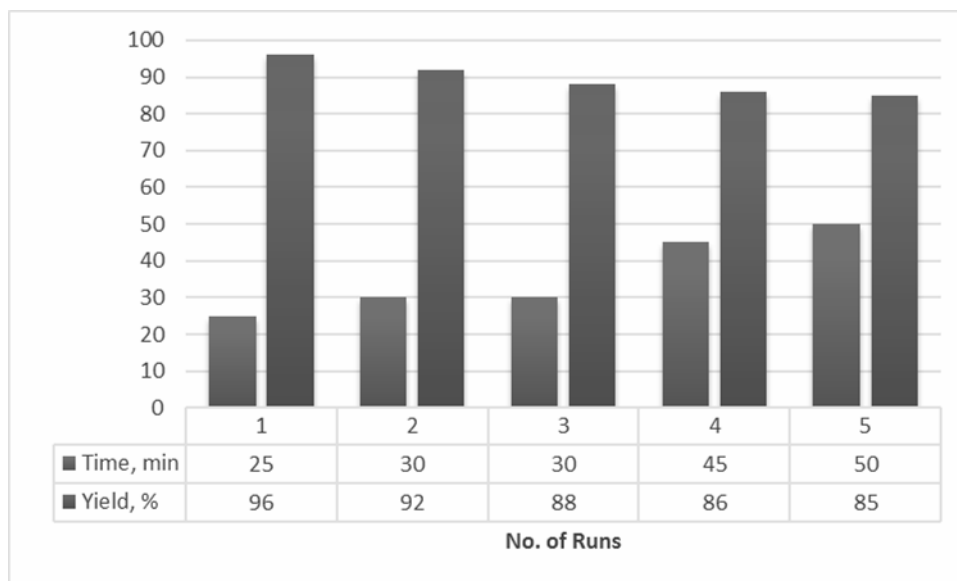


Fig. 4 – Reusability of the catalyst in the reaction of Dimedone (2 mmol) and benzaldehyde (1 mmol) at 80 °C under solvent-free conditions.

Table 3

Comparison of Caffeine-H₂SO₄ with reported catalysts in the reaction of Dimedone with *p*-Nitrobenzaldehyde

Entry	Catalyst/Condition	Catalyst loading (mol %)	Time, hr	Yield, %	Ref.
1	TBAHS/ Aqueous dioxane reflux	10	3	94	12
2	PPA-SiO ₂ /Solvent-free 140°C	10	0.5	70.7	14
3	PMA-SiO ₂ /CH ₃ CN reflux	0.1	5	90	15
4	HPWA/MCM-41 /Ethanol 90°C	20	5	87	17
5	Acidic MCM-41/ CH ₃ CN reflux	0.1 g	0.33	95	19
6	TSIL/ Water reflux	10	1	91	16
7	Caffeine-H ₂ SO ₄	10	0.5	97	This work

CONCLUSION

In conclusion, a simple, and green protocol for the synthesis of 1,8-dioxo-octahydro-xanthenes has been presented here through the one-pot condensation reaction of aromatic aldehydes and dimedone in the presence of Caffeine-H₂SO₄ as a novel environmentally safe bio-based acidic catalyst under solvent-free conditions. This method offers several advantages including high yields, recyclable catalyst, short reaction times, easy work-up and green reaction conditions.

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