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CsF mediated rapid condensation of 1,3-cyclohexadione with aromatic aldehydes: Comparative study of conventional heating *vs*. ambient temperature

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Abstract

A mild, efficient and high yielding protocol for the synthesis of 2,2′-arylmethelene dicyclohexane-1,3-dione derivatives at room temperature and 9-aryl-1,8-dihydrooctahydroxanthene at conventional heating using cesium fluoride as a catalyst is reported. The major advantages of this reaction are excellent yield, very short reaction time and use of inexpensive catalyst.

Keywords: Aromatic aldehydes; 1,3-Cyclohexadione; Cesium fluoride

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The polyfunctionalized benzopyrane ring system is one of the most important classes of organic compounds found in numerous natural products [1] and drugs [2]. Benzopyrane based xanthenes have been shown to be an increasingly important class of biological active compounds for the access of potential biodegradable agrochemicals [3] and pharmaceutical products, such as anti-inflammatory, antiviral, anticancer, anticoagulant, antianaphylactin and diuretic [4]. Furthermore, these compounds have been investigated as cosmetic, pigments, antispam and fluorescent fuel [5]. Moreover, tetraketone derivatives have been used as versatile synthon since they have stimulated the synthesis of acridines [6], xanthenes, thiaxanthenes and inherent reactive inbuilt pyrane ring [7]. In addition, tetraketone and xanthene derivatives having two keto functional groups at 1st and 8th position act as antimalerial agents [8].

Recently, several methods for obtaining tetraketone [9] and 1,8-dihydrooctahydroxanthene derivatives [10] are developed, such as in the presence of strong protonic acids [11], ionic liquids [12], Lewis acids [13] and heterogeneous catalysts [14] have been reported. However, some of these methodologies have not been entirely satisfactory, with disadvantage such as harsh reaction conditions, low yields, use of stoichiometric or relatively expensive reagents and difficulties in work up. Therefore, we consider that it is worthwhile to develop methods of preparing 2,2′-arylmethylene dicyclohexane-1,3-dione and 9-aryl-1,8-dihydrooctahydroxanthene derivatives, which works at room temperature and conventional heating using cesium fluoride as a catalyst. We have investigated the potential of CsF to obtain the 2,2′-arylmethylene dicyclohexane-1,3-dione and 9-aryl-1,8-dihydrooctahydroxanthene derivatives by the condensation of aromatic aldehydes with 1,3-cyclohexanedione. The effect of reaction condition has also been investigated. The present study described below has the advantage of yielding 2,2′-arylmethylene dicyclohexane-1,3-dione derivatives at ambient temperature [15] and 9-aryl-1,8-dihydrooctahydroxanthene derivatives at conventional heating [16].

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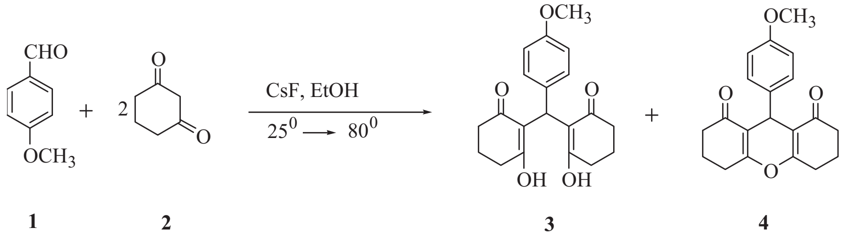


Scheme 1.

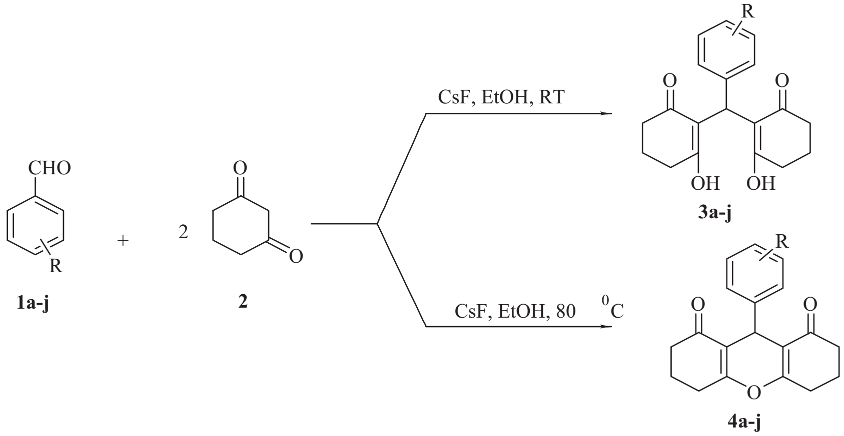
1. Experimental

All reactions were performed with commercially available reagents. All liquid reagents were distilled and dry before use. Melting points were determined by open tube capillary method and were uncorrected. IR spectra were obtained on Shimadzu FTIR-spectrometer (KBr Pellets), ^{1}H NMR spectra were recorded on a Bruker advance 400 spectrometer (400 MHz) in $CDCl_3$ using TMS as internal reference and mass spectra were recorded under ESI mode.

2. Result and discussion

The aldehyde **1** was selected as probe aldehyde to optimize the reaction conditions (Scheme 1) and the results are listed in Table 1. At first the reaction was carried out in the absence of catalyst, the product **3** (Table 1, entries 1 and 2) resulting as a lone product with low yield from longer reaction time. However, the addition of a catalytic amount of CsF resulted in formation of product **3** with 95% yield in 30 min at room temperature. This clearly indicates that the catalytic effect of CsF on the synthesis of **3**. With these results in hand we investigated catalytic amount required for the reaction, and found 10 mol% of CsF (Table 1, entry 3) catalyst gives excellent yield. As the temperature of the reaction increased from 25 °C to 50 °C, resulted in a formation of products **3** and **4** (Table 1, entry 4). As the temperature of the reaction was increased up to 80 °C, the yield of **4** was changed markedly, with maximum yield (Table 1, entry 5). The distinctive feature of the reaction is that **3** and **4** obtained with very short reaction times. Excess amount of the catalyst did not improve the yield to a greater extent (Table 1, entry 7).

Therefore, it can clearly be seen that the best conditions for reactions were 10 mol% of CsF at room temperature and at 80 °C affords only product **3a–j** and **4a–j**, respectively (Scheme 2). After optimizing the reaction conditions, we next examined the generality of these conditions to other substrates using several aromatic aldehydes with electron withdrawing or donating groups and 1,3-cyclohexanedione (Table 2). The catalyst plays crucial role in the success of the reaction in terms of the rate and the yields. The electron withdrawing groups on aromatic ring require short reaction time as compared to electron donating groups but did not show effects in terms of yields under these reaction conditions. It was found that yields of **3** and **4** were very good to excellent. 2,2′-Arylmethylene dicyclohexane-1,3-



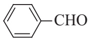
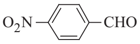
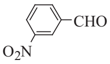
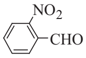
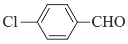
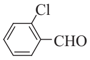
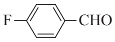
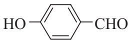
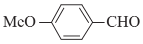
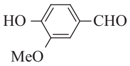
Scheme 2.

Table 1
Optimization of reaction conditions of 1,3-cyclohexadione with 4-methoxybenzaldehyde.

Entry	CsF (mol%)	Temp. (°C)	Time (h)	Yields (%)[a]	
				3	4
1	0	25	15	13	0
2	0	80	10	41	5
3	10	25	0.5	95	0
4	10	50	4	32	59
5	10	80	1.5	0	92
6	5	80	2	0	71
7	15	80	2	0	92

[a] Isolated yield.

Table 2
CsF mediated rapid condensation of 1,3-cyclohexadione with aromatic aldehydes[a].

Entry	Aldehyde	Product[b]	Reaction time (yield%)[c]
1		**3a**	15 min (91)
		4a	45 min (90)
2		**3b**	10 min (93)
		4b	40 min (92)
3		**3c**	10 min (96)
		4c	40 min (90)
4		**3d**	15 min (91)
		4d	60 min (84)
5		**3e**	25 min (87)
		4e	85 min (89)
6		**3f**	20 min (91)
		4f	80 min (87)
7		**3g**	22 min (85)
		4g	80 min (82)
8		**3h**	35 min (84)
		4h	95 min (88)
9		**3i**	25 min (95)
		4i	90 min (92)
10		**3j**	30 min (86)
		4j	80 min (87)

[a] Reactions conditions: 1,3-cyclohexadione (2 mmol), aldehyde (1 mmol), CsF (10 mol%).

[b] All compounds were characterized by using IR, NMR and MS and mp.

[c] Isolated yield.

dione and 9-aryl-1,8-dihydrooctahydroxanthene have been characterized by FT-IR, NMR and mass spectral techniques [17].

3. Conclusion

In conclusion, 2,2′-arylmethylene dicyclohexane-1,3-dione and 9-aryl-1,8-dihydrooctahydroxanthene have been synthesized successfully using CsF (10 mol%) as a catalyst. The product **3** was obtained at ambient temperature and **4** at reflux condition in very good to excellent yields.

Acknowledgments

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(d) T.S. Jin, J.S. Zhang, A.Q. Wang, et al. Synth. Commun. 35 (2005) 2339;
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[15] *General method for synthesis of* (**3**)*:* A mixture of an aromatic aldehyde (1.0 mmol), 1,3-cyclohexadionone (2.0 mmol) and 10 mol% CsF in ethanol (10 mL) was stirred at room temperature for 15–35 min. The progress of the reaction was monitored by thin-layer chromatography, TLC (eluent, ethyl acetate–hexane 1:1) after completion of the reaction, the white solid precipitated out from ethanol, filtered, washed with water (25 mL) and purified by recrystallization from ethanol.
[16] *General method for synthesis of* (**4**)*:* A mixture of an aromatic aldehyde (1.0 mmol), 1,3-cyclohexadionone (2.0 mmol) and 10 mol% CsF in ethanol (10 mL) was heated at 80 °C for 60–120 min. The progress of the reaction was monitored by thin-layer chromatography, TLC (eluent, ethyl acetate–hexane 2:1) after completion of the reaction, ethanol was removed by reduced pressure. Suspended white solid in 3 mol/L HCl, filtered, washed with water (25 mL) and purified by recrystallization from ethanol.
[17] Spectral data for the selected compounds: 2,2′-((3-nitrophenyl)methylene)-dicyclohexane-1,3-dione (**3c**): ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.30 (br s, 2H, OH), 8.01 (d, 1H, J = 8.0 Hz, ArH), 7.57 (s, 1H, ArH), 7.35 (m, 2H, ArH), 5.50 (s, 1H, CH), 2.74–2.58 (m, 4H, CH_2), 2.52–2.36 (m, 4H, CH_2), 2.12–2.04 (m, 4H, CH_2); IR (KBr, cm^{-1}): 3316, 2955, 1720, 1627, 1516; MS(ESI): *m/z* 357.1(M^+); slight yellow solid; M.P. 196–198 °C. 9-(3-Nitrophenyl)-1,8-dioxooctahydroxanthene (**4c**): ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.0 (d, 1H, J = 7.8 Hz, ArH), 7.86 (s, 1H, ArH), 7.43 (m, 2H, ArH), 4.88 (s, 1H, CH), 2.75–2.59 (m, 4H, CH_2), 2.39–2.32 (m, 4H, CH_2), 2.12–1.96 (m, 4H, CH_2); IR (KBr, cm^{-1}): 2953, 2896, 1658, 1517, 1328; MS(ESI): *m/z* 339.1(M^+); white solid; M.P. 286–288 °C. 2,2′-((4-Methoxyphenyl)methylene)-dicyclohexane-1,3-dione (**3i**): ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.35 (br s, 2H, OH), 7.08 (t, 2H, J = 8.2 Hz, ArH), 6.81 (d, 2H, J = 8.4 Hz, ArH), 5.45 (1, 1H, CH), 3.8 (s, 3H, OCH_3), 2.72–2.54 (m, 4H, CH_2), 2.52–2.36 (m, 4H, CH_2), 2.1–1.98 (m, 4H, CH_2); IR (KBr, cm^{-1}): 3390, 2958, 1722, 1602, 1510; MS(ESI): *m/z* 342.1(M^+); off-white solid; M.P. 180–182 °C. 9-(4-Methoxyphenyl)-1,8-dioxoocta-hydroxanthene (**4i**): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22 (d, 2H, J = 8.1 Hz, ArH), 6.77 (d, 2H, J = 8.1 Hz, ArH), 4.75 (s, 1H, CH), 3.73 (s, 3H, OCH_3), 2.63–2.55 (m, 4H, CH_2), 2.37–2.30 (m, 4H, CH_2), 2.03–1.98 (m, 4H, CH_2); IR (KBr, cm^{-1}): 2956, 2360, 1720, 1658, 1510; MS(ESI): *m/z* 324.1(M^+); white solid; M.P. 200–202 °C.