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RESEARCH ARTICLE

A Facile, One Pot, Solvent Free Synthesis of 14-Alkyl or Aryl-14*H*-dibenzo[*a,j*]xanthenes and 12-Aryl/alkyl-8,9,10,12-tetrahydrobenzo[*a*]xanthen-11-one Derivatives

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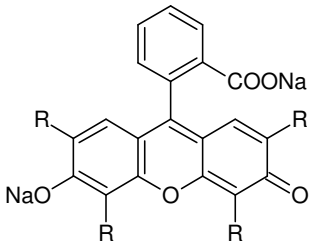
Abstract: An efficient method for the one-pot synthesis of 14-alkyl or aryl-14*H*-dibenzo[*a,j*]xanthenes, by the condensation of aldehydes and β-naphthol under solvent free conditions using silica supported copper(II) sulphate, has been described. This strategy is further extended to three component coupling of aldehydes, β-naphthol and cyclic 1,3-dicarbonyl compounds for the synthesis of 12-aryl-8,9,10,12-tetrahydrobenzo[*a*]xanthen-11-one derivatives. The present catalytic system is recyclable and can be reused without greater loss of reactivity.

Keywords: Xanthenes, Naphthol, Solvent free reaction, Supported catalyst, Copper(II) sulphate

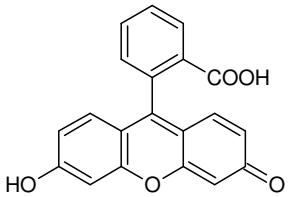
Introduction

Oxygen heterocycles especially xanthenes are an important class of heterocycles[1]. These compounds have very interesting spectroscopic properties resulting from their extended conjugation and as such have many applications in laser methodologies[2]. Xanthenes derivatives are valuable colouring magents *viz.* eosin **1** (acid red), used in inks, lipsticks, nail varnishes as well as used to dye silk and paper, while erythrosine **2** is a certified food additive, in addition to its value as a biological stain. Aminoxanthene derivatives like Pyronine B and Pyronine G are used as bacterial stains and also used as an analytical reagent for many transition metals. These compounds are further crowned to being sub-set of luminescent sensors[3]. Fluorescein **3** (acid yellow) is one of the best known xanthene dye, used as a location marker for aircrafts lost at sea, as a tracer to detect source of contamination in drinking water and to detect abrasions of the cornea.

Xanthenes derivatives are also promising sensitizers in photodynamic therapy (PDT), a well known method of controlling the localized tumours[4]. Molecules of this class like methantheline and propantheline are used for the treatment of ulcers, gastrointestinal disorders and gastric secretion regulation while mubromin is known for its antibacterial and antiseptic properties. In addition, a variety of biological activities such as, anti-inflammatory[5], antiviral[6], muscarinic receptor antagonist[7], cancer chemotherapy[8], thrypanothione reductase inhibitor[9], MGiuRI enhancer[10] and CCR_1 antagonist[11], bodes well on this scaffold.



1, R = Br; **2,** R = I



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Experimental

Melting points were determined in open capillary and compared with authentic samples. IR spectra were obtained by using Perkin-Elmer 237B spectrophotometer in KBr discs. ^{1}H NMR spectra were recorded in Varian Gemini 300 spectrophotometer (300 MHz) using tetramethylsilane (TMS) as internal standard. Copper(II) sulphate used was procured from SD Fine Chemicals Pvt. Ltd. All other chemical were purified by distillation or crystallization prior to use.

Typical experimental procedure for the synthesis of 14H-dibenzo[a,j]xanthene (**3**)

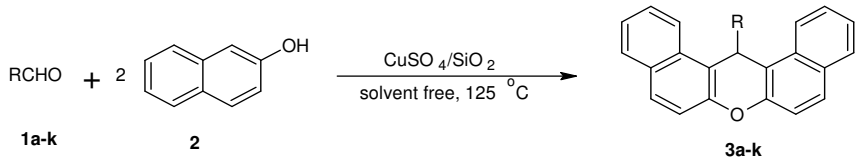
In a typical example, benzaldehyde (2 mmol), β-naphthol (4 mmol) and silica supported copper(II) sulphate (0.166 mg, 0.1 mmol) were mixed and grinded in a mortar for 10 minutes at room temperature. Then this reaction mixture was heated at 125 ^{o}C for the stipulated time (Table 2). After the completion of reaction (vide TLC), reaction mixture was cooled to room temperature and extracted with ethyl acetate (3x10 mL). Organic extract was washed with water (20 mL) and solvent was removed under reduced pressure. The solid thus obtained was recrystallised with ethanol to afford colourless crystals, 14-phenyl-14*H*-dibenzo[*a,j*] xanthene **3a**, 93% yield, mp 184-85 °C (Lit.[12] mp 185 °C) (entry 1, Table 2). Similarly, other aldehydes **1b-k** were reacted with β-naphthol to afford various xanthene derivatives **3b-k** (Table 2).

Typical experimental procedure for the synthesis of tetrahydrobenzo[a]xanthen-11-ones (**5**)

In a typical reaction, benzaldehyde (2.0 mmol), β-napthol (2.0 mmol), dimedone (2.0 mmol) and $CuSO_4/SiO_2$ (5 mol%) were mixed and grinded in mortar for 10 min. Then this reaction mixture was transferred to reaction vessel and heated at 125 ^{o}C for the stipulated time (Table 3). After the completion of reaction (vide TLC), reaction mixture was cooled to room temperature and extracted with ethyl acetate (3x10 mL). Organic extract is washed with water (20 mL) and solvent is removed under reduced pressure. The solid thus obtained was recrystallised with ethanol to afford 9,9-dimethyl-12-phenyl-8,9,10,12-tetrahydrobenzo [*a*]xanthen-11-one **5a**, in 86% yield, 152-53 °C (Lit.[13] mp 154-55 °C) (entry 1, Table 3). Similarly, other derivatives **5b-h** are also obtained in good to excellent yield (Table 3).

Results and Discussion

Owing to these attractive properties, efficient syntheses for this class of heterocycles are of interest to synthetic chemists. Several methods reported for the synthesis of xanthenes includes aryne cycloaddition on to phenols[14], cyclodehydration[15], intramolecular coupling of aldehydes and ketones[16], carbon monoxide[17], protected aldehydes[18], formamide[19], 2-napthol-1-methanol[20] and condensation of β-naphthols with aldehydes[21,22]. Some of these methods have one or the other limitation like use of toxic or corrosive materials, poor yield, prolonged reaction time, use of strong acids, harsh reaction conditions and use of stoichiometric reagents. Hence development of a clean, facile and efficient process for the synthesis of these important molecules of commercial significance is highly desirable. Therefore, in continuation to our investigations on the synthesis of oxygen heterocycles[23], we describe here an efficient and facile method for the production of xanthenes using $CuSO_4/SiO_2$[24] under solvent free conditions under conventional as well as microwave heating (Scheme 1).



Scheme 1. Synthesis of 14*H*-dibenzo[*a,j*]xanthenes

In the course of optimization of reaction conditions, 5 mol% of catalyst was found optimum to catalyse this condensation. The catalyst recovered, dried and reused without quantitative loss of yield (Table 1, entry 5-7). Use of higher amount of catalyst (10 mol%) did not improve the yields (Table 1, entry 8) while decrease in amount of catalyst decreases the yield (Table 1, entry 1-3). When the reaction was carried out in solvent medium (Table 1, entry 9-11), it completed in longer time with considerable fall in yield.

Table 1. Catalytic efficacy of $CuSO_4/SiO_2$for the synthesis of 14*H*-dibenzo[*a*]xanthenes

Entry	Amount of catalyst used, mol%	Time/min.	Yield/%
1	1	200	32
2	2	120	54
3	3	60	67
4	5	25	93[a]
5	5	25	92[b]
6	5	25	90[c]
7	5	30	84[d]
8	10	25	92
9	5	150	66[e]
10	5	150	71[f]
11	5	120	61[g]

[a] 1st run; b 2nd run; [c] 3rd run, [d] 4th run, [e] in MeOH; [f] in EtOH and [g] in toluene

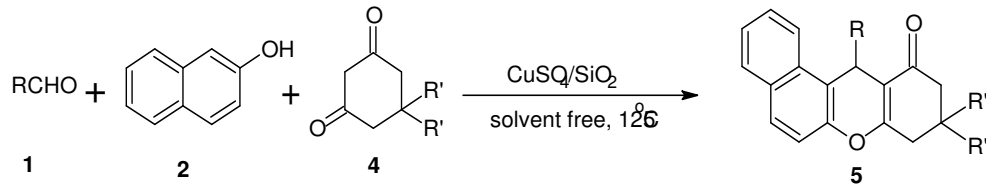
Catalyst worked well with aromatic aldehydes (entry 1-9, Table 2) as well as for aliphatic aldehydes (entry 10-12, Table 2), giving various xanthene derivatives in 82-94% yields. This method tolerates various functionalities like nitro, ether, halogen *etc*. on the aldehyde. When the reaction was carried out under microwave irradiation, equivalent results were obtained.

Encouraged by these results, this strategy is further extended to a three component coupling of aldehyde, β-naphthol and cyclic-1,3-dicarbonyl compounds (Scheme 2) to afford 12-aryl-8,9,10,12-tetrahydrobenzo[*a*]xanthen-11-one derivatives in excellent yields.

Table 2. $CuSO_4/SiO_2$ mediated synthesis of 14-alkyl or aryl-14*H*-dibenzo[*a.j*]xanthenes

Entry	Aldehyde	Product[a]	Time, min	Yield[b], %	m.p. °C
1	C_6H_5	**3a**	25	93	184-85
2	4-$CH_3C_6H_4$	**3b**	30	91	227-29
3	4-BrC_6H_4	**3c**	25	91	295-97
4	4-ClC_6H_4	**3d**	25	94	287-89
5	4-$OCH_3C_6H_4$	**3e**	30	89	203-04
6	4-$NO_2C_6H_4$	**3f**	25	92	309-10
7	3-BrC_6H_4	**3g**	35	88	190-02
8	3-$NO_2C_6H_4$	**3h**	30	91	210-11
9	2-ClC_6H_4	**3i**	35	90	214-15
10	CH_3CHO	**3j**	35	82	172-73
11	CH_3CH_2CHO	**3k**	35	83	112-13

[a]*Products were characterized by comparison of their melting point and spectral (IR, ^1H NMR) data.*
[b]*Isolated yields*



Scheme 2. Synthesis of tetrahydrobenzo[*a*]xanthen-11-one

Table 3. Synthesis of tetrahydrobenzo[*a*]xanthen-11-one derivatives catalysed by $CuSO_4/SiO_2$

S.No.	R	R'	Product	Time, min.	Yield, %	m.p. °C
1	C_6H_5	Me	**5a**	80	86	151-53
2	4-Cl-C_6H_4	Me	**5b**	75	89	182-83
3	4-NO_2-C_6H_4	Me	**5c**	75	91	178-80
4	4-OCH_3-C_6H_4	Me	**5d**	90	84	204-05
5	4-OH-C_6H_4	Me	**5e**	90	78	223-25
6	3-NO_2-C_6H_4	Me	**5f**	75	85	168-70
7	2-Cl-C_6H_4	Me	**5g**	110	77	179-80
8	2-NO_2-C_6H_4	Me	**5h**	110	76	223-25

Reactions proceed smoothly with aldehydes bearing electron withdrawing as well as electron donating substituents (Table 3). Products are obtained by simple work up. Catalyst efficacy is fairly general and afforded the resultant products in good to excellent yields.

Characterization and spectral data for some selected compounds

14-Phenyl-14H-dibenzo[a,j]xanthene (***3a***)

Mp 184-85 °C. IR (KBr): 3030, 1612, 1410, 1242 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 6.75 (s, 1 H), 7.10-8.10 (m, 17 H). Anal Calc. for $C_{27}H_{18}O$: C, 90.47; H; 5.06. Found: C, 90.55; H; 4.98.

14-(4-Methylphenyl)-14H-dibenzo[a,j]xanthene (***3b***)

Mp 227-29 °C. IR (KBr): 3038, 1618, 1240 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ =2.30 (s, 3H), 6.55 (s, 1H), 7.15-7.95 (m, 16H). Anal Calc. for $C_{28}H_{20}O$: C, 90.29; H; 5.41. Found: C, 90.35; H; 5.43.

14-(4-Methoxyphenyl)14-H-dibenzo[a,j]xanthene (***3e***)

Mp 203-04 °C. IR (KBr): 3035, 1621, 1581, 1252. cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 3.50 (s, 3 H), 6.45 (s, 1 H), 6.73 (d, *j* = 9.3 Hz, 2H), 7.36-7.92 (m, 12 H), 8.36 (d, *j* = 9.3 Hz, 2 H). Anal Calc. for $C_{28}H_{20}O_2$: C, 86.57; H; 5.19. Found: C, 86.49; H; 5.18.

14-(4-Nitrophenyl)-14H-dibenzo[a,j]xanthene (***3f***)

Mp 309-10 °C. IR (KBr): 3070, 1615, 1540, 1355, 1245. cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.20-7.90 (m, 12H), 8.15 (d, *J* = 9.0 Hz, 2H), 8.55 (d, *j* = 9.0 Hz, 2H). Anal Calc. for $C_{27}H_{17}NO_3$: C, 80.38; H, 4.25; N, 3.47. Found: C, 80.45; H, 4.22, N, 3.46.

14-Methyl-14H-dibenzo[a,j]xanthene (***3j***)

Mp 172-73 °C. IR (KBr): 3045,2901, 1615, 1221 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.64 (d, *J* = 6.1Hz, 3H), 5.60 (q, *J* = 6.1 Hz, 1H) 7.09-7.97 (m, 12H). Anal Calc. for $C_{22}H_{16}O$: C, 89.16; H; 5.44. Found: C, 89.35; H; 5.39.

9,9-Dimethyl-12-phenyl-8,9,10,12-tetrahydro-11H-benzo[a]xanthen-11-one (***5a***)

Mp. 152-153 ^oC; IR (KBr): 3055, 2954, 2884, 1651, 1374, 1229, 1178, 1076, 811 cm^{-1}; δ 7.99 (d, J=8.1 Hz, 1H), 7.78–7.74 (m, 2H), 7.42–7.04 (m, 8H), 5.70 (s, 1H), 2.57 (s, 2H), 2.33 (d, J¼16.2 Hz, 1H), 2.26 (d, J¼16.2 Hz, 1H), 1.11 (s, 3H), 0.96 (s, 3H). Anal Calc. for $C_{25}H_{22}O_2$: C, 84.72; H; 6.26. Found: C, 84.65; H; 6.24.

12-(4-Chlorophenyl)-9,9-dimethyl-9,10-dihydro-8H-benzo[a]xanthen-11-one (***5b***)

Mp. 180–182 ^oC; IR (KBr): 3072, 2925, 1645, 1374, 1226, 1174, 1088 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.90 (d, J=8.1 Hz, 1H), 7.79–7.75 (m, 2H), 7.45–7.11 (m, 7H), 5.67 (s, 1H), 2.56 (s, 2H), 2.34 (d, J=16.2 Hz, 1H), 2.26 (d, J=16.2 Hz, 1H), 1.12 (s, 3H), 0.96 (s, 3H). Anal Calc. for $C_{25}H_{21}ClO_2$: C, 77.21; H; 5.44. Found: C, 77.34; H; 5.38.

9,9-Dimethyl-12-(4-nitrophenyl)-9,10-dihydro-8H-benzo[a]xanthen-11-one (***5c***)

Mp. 178–180 ^oC; IR (KBr): 3077, 2934, 1645, 1597, 1516, 1377, 1343, 1225, 1177, 1026, 827 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.04 (d, J=8.4 Hz, 2H), 7.82–7.79 (m, 3H), 7.52–7.33 (m, 5H), 5.81 (s, 1H), 2.59 (s, 2H), 2.36 (d, J=16.2 Hz, 1H), 2.26 (d, J=16.2 Hz, 1H), 1.13 (s, 3H), 0.94 (s, 3H). Anal Calc. for $C_{25}H_{21}NO_4$: C, 75.17; H; 5.30; N, 3.51. Found: C, 75.24; H; 5.21; N, 3.42.

12-(4-Methoxyphenyl)-9,9-dimethyl-9,10-dihydro-8H-benzo[a]xanthen-11-one (***5d***)

Mp. 204–205 ^oC; IR (KBr): 3057, 2949, 1643, 1227, 1172, 1024 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.99 (d, J=8.1 Hz, 1H), 7.77–7.72 (m, 2H), 7.44–7.22 (m, 5H), 6.70 (d, J=8.4 Hz, 2H), 5.65 (s, 1H), 3.68 (s, 3H), 2.55 (s, 2H), 2.33 (d, J=16.2 Hz, 1H), 2.26 (d, J=16.2 Hz, 1H), 1.11 (s, 3H), 0.97 (s, 3H). Anal Calc. for $C_{26}H_{24}O_3$: C, 81.22; H; 6.29.Found: C, 81.14; H; 6.22.

12-(4-Hydroxyphenyl)-9,9-dimethyl-9,10-dihydro-8H-benzo[a]xanthen-11-one (***5e***)

Mp. 223–225 ^oC; IR (KBr): 3305, 2957, 1638, 1572, 1378, 1225, 1176, 1026 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.98 (d, J=8.1 Hz, 1H), 7.78–7.73 (m, 2H), 7.45– 7.15 (m, 5H), 6.61 (d, J=8.4 Hz, 2H), 5.63 (s, 1H), 5.49 (s, 1H), 2.56 (s,2H), 2.34 (d, J=16.2 Hz, 1H), 2.27 (d, J=16.2 Hz, 1H), 1.12 (s, 3H), 0.97 (s, 3H). Anal Calc. for $C_{25}H_{22}O_3$: C, 81.06; H, 5.99. Found C, 81.12; H, 5.91.

9,9-Dimethyl-12-(3-nitrophenyl)-9,10-dihydro-8H-benzo[a]xanthen-11-one (***5f***)

Mp. 168–170 ^oC; IR (KBr): 3071, 2955, 1649, 1528, 1372, 1356, 1224, 1172, 1025, 809 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.10 (s, 1H), 7.95–7.80 (m, 5H), 7.47–7.35 (m, 4H), 5.81 (s, 1H), 2.61 (s, 2H), 2.36 (d, J=16.2 Hz, 1H),2.26 (d, J=16.2 Hz, 1H), 1.13 (s, 3H), 0.95 (s, 3H). Anal Calc. for $C_{25}H_{21}NO_4$: C, 75.17; H; 5.30; N, 3.51. Found: C, 75.28; H; 5.24; N, 3.48.

12-(2-Chlorophenyl)-9,9-dimethyl-9,10-dihydro-8H-benzo[a]xanthen-11-one (***5g***)

Mp. 179–180 ^{o}C; IR (KBr): 3075, 2930, 1648, 1372, 1229, 1179, 1030, 748 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.23 (d, J=8.4 Hz, 1H), 7.76–7.72 (m, 2H), 7.49–7.26 (m, 5H), 7.07–6.96 (m, 2H), 5.98 (s, 1H), 2.60 (s, 2H), 2.34 (d,J=16.2 Hz, 1H), 2.24 (d, J=16.2 Hz, 1H), 1.13 (s, 3H), 0.99 (s, 3H). Anal Calc. for $C_{25}H_{21}ClO_2$: C, 77.21; H; 5.44. Found: C, 77.28; H; 5.41.

9,9-Dimethyl-12-(2-nitrophenyl)-9,10-dihydro-8H-benzo[a]xanthen-11-one (***5h***)

Mp. 223–225 ^{o}C; IR (KBr): 3069, 2957, 2926, 1651, 1526, 1369, 1227, 1170, 1028, 823 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.56 (d, J=8.1 Hz, 1H), 7.86–7.77 (m, 3H), 7.46–7.03 (m, 6H), 6.58 (s, 1H), 2.60 (d, J=17.4 Hz, 1H), 2.52 (d, J=17.4 Hz, 1H), 2.29 (d, J=16.2 Hz, 1H), 2.19 (d, J=16.2 Hz, 1H), 1.11 (s, 3H), 0.86 (s, 3H). Anal Calc. for $C_{25}H_{21}NO_4$: C, 75.17; H; 5.30; N, 3.51. Found: C, 75.31; H; 5.17; N, 3.39.

Conclusion

In conclusion, a simple, facile and environmentally benign method using $CuSO_4/SiO_2$, as an inexpensive, easily available and non-corrosive reagent, for the synthesis of 14*H*-dibenzo[*a.j*] xanthenes and tetrahydrobenzo[*a*]xanthen-11-one derivatives in quantitative yield, have been described. The notable advantages of the present method are operational simplicity, availability of reagent, short reaction times, easy work-up and wider scope.

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