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ORIGINAL ARTICLE

POLY(ETHYLENE)GLYCOL AS AN EFFICIENT AND CONVENIENT SOLVENT FOR THE SYNTHESIS OF 14-SUBSTITUTED-14H-DIBENZO [A, J] XANTHENES AT ROOM TEMPERATURE

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Abstract:

An efficient one-pot method for the synthesis of 14-substituted-14H-dibenzo[a,j]xanthenes using cyanuric chloride as a catalyst in the presence of poly(ethylene)glycol at room temperature is described. Excellent yield of products and environment friendly experimental procedure are the advantages of this method.

Keywards:*Xanthenes, poly(ethylene)glycol, cyanuric chloride (TCT), room temperature, excellent yield.*

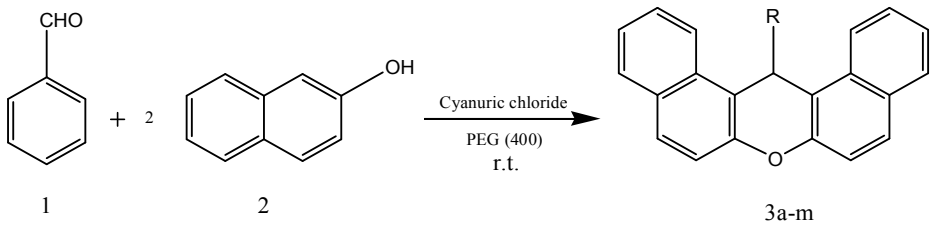
1. INTRODUCTION

In recent years, the synthesis and pharmacology of xanthenes have been extensively investigated due to their wide range of biological activities[1-3]. They display many activities such as antiviral[1], antibacterial[2] and anti-inflammatory activities[3], finds use in biodegradable agrochemicals[4], cosmetics and pigments[5], fluorescent materials[6], luminescent sensors[7], and in laser technologies[8]. It is also important to mention that benzoxanthene derivatives have shown promising activity as sensitizer in photodynamic therapy (PDT) as well as controlling localized tumors [9- 10].

Literature survey indicated a large number of reports on the synthesis of xanthenes including condensation of aldehydes and dimedone or cyclohexane-1,3-dione[11], intramolecular coupling of aldehydes and ketones[12], cyclodehydration[13], the reaction of β-naphthol with formamide[14], β-naphthol-1-methanol[15] and carbon monoxide[16]. But these methods are limited due to harsh reaction conditions, long reaction time, low yields, use of excess reagents and catalyst, use of volatile toxic solvents and need of special apparatus. To overcome these limitations, recently, the reaction has been improved by mixing β-naphthol with aldehydes in the presence of various catalysts such as Amberlyst-15[17], LiBr[18], sulfamic acid[19], p-TSA[20], I_2[21], sulphonated polyethylene glycol[22] and DABCO[23]. These methods are also suffers one or the other disadvantages such as tedious experimental procedure, use of hazardous reagent, high

temperature and high loading of catalyst. Consequently, there is scope for further renovation of such synthetic methods, which avoids both harsh reaction conditions and high loading of catalyst.

Poly(ethylene)glycols (PEGs) has a number of benign characteristics which make them green solvents for organic synthesis[24-26]. Herein, we report a new, simple and efficient method for the synthesis of xanthenes using PEG-400 as solvent medium in presence of cyanuric chloride at room temperature (Scheme 1).

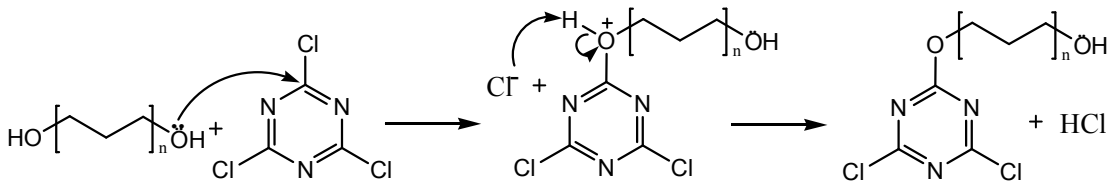


Scheme 1

2. RESULT AND DISCUSSION

In earlier reports we showed the efficiency of 2, 4, 6-Trichloro-1, 3, 5-Triazine (TCT) for various transformations[27-30]. In continuation of our research work in the development of synthetic methods using cyanuric chloride, we report herein an efficient, simple, and convenient procedure for the synthesis of benzoxanthene derivatives using PEG-400 as a green solvent at room temperature.

Initially, we optimized the amount of cyanuric chloride as a catalyst required for a model reaction of 4-chlorobenzaldehyde (2 mmol),β-naphthol (4 mmol) and PEG-400 (2g). When this reaction mixture was stirred without catalyst for 12 hours (Table 1, entry 1) even trace mount of the product did not formed. We then started to use cyanuric chloride as a catalyst for the reaction, when the amount of catalyst used is less than 4 mol%, low to moderate yield of corresponding benzoxanthene is obtained (Table 1, entries 2-4). With 4 mol % of the catalyst, the good yield of benzoxanthene was obtained (Table 1, entry 5). While the use of 5 (200 mmol) and PEG-400 (100g) by using TCT (1.37 mol%) mol% catalyst leads to the excellent yield of the product (Table 1, entry 6). TCT (5mol %) was the optimum amount of catalyst whereas, higher loading of catalyst did not improve the yields (Table 1, entries 7-9).
Poly(ethylene)glycol is an appropriate green solvent in which TCT generates (insitu) dry HCl to catalyze the synthesis of 14-aryl or alkyl-14-*H*-dibenzo[*a,j*] xanthenes at room temperature. A plausible mechanism is shown in scheme 2.



Scheme 2

Using the best conditions reported in Table 1, we then continued to study the reaction by using verity of aromatic (Table 2, entries 1-10) as well as aliphatic aldehydes (Table 2, entries 11-13). The results summarized in Table 2 indicating that the method is general and tolerate verity of groups present in aldehydic moiety. Moreover, these reactions are clean with excellent yields. As compared to recently reported methods[31-32], involving the use of higher loading of wet cyanuric chloride as a catalyst or PEG-400 alone at 120 ^{0}C, the present protocol is superior as it works with half quantity of catalyst at room temperature.

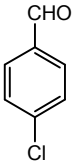
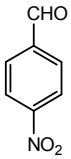
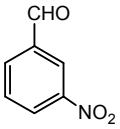
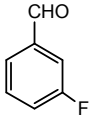
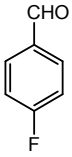
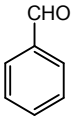
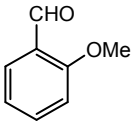
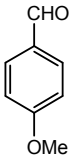
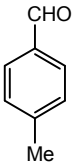
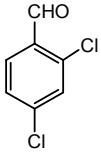
The advantages of the present protocol are: (i) use of commercially available inexpensive catalyst (ii) use of PEG-400 as an environmentally friendly solvent (iii) mild reaction conditions (iv) method works well on 100 mmol scale therefore, this protocol may be applicable on large scale synthesis of these bioactive compounds (Table 1, entry 7) (v) filtration followed by recrystllization provides analytically pure compounds therefore, purification of the product using column chromatography is not required.

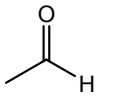
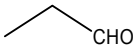
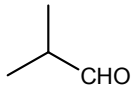
Table1. Comparison of the catalytic efficiency of TCT with some reported catalysts for the synthesis of *14H*-(4-chlorophenyl)-dibenzo[*a,j*]xanthenes.

Entry	Catalyst (g)	Solvent	Temp.(^{0}c)	Time(h)	Yield[a] (%)	Ref.
1	----	PEG-400	rt	12	----	-
2	TCT (0.001)	PEG-400	rt	12	30	-
3	TCT (0.002)	PEG-400	rt	6	45	-
4	TCT (0.003)	PEG-400	rt	2.30	67	-
5	TCT (0.005)	PEG-400	rt	1.30	94	-
7	TCT (0.005)	PEG-400	rt	1.30	93[b]	-
8	TCT (0.006)	PEG-400	rt	1.30	93	-
9	TCT (0.007)	PEG-400	rt	1.30	92	-
10	TCT (0.008)	PEG-400	rt	1.30	90	-
11	Silica sulfuric acid	Solvent-free	80	0.45	86	10
12	Sulfamic acid	Solvent-free	125	11	92	12
13	$HClO_4$-SiO_2	Solvent-free	125	0.08	92	11
14	$HClO_4$-SiO_2	1,2-dichloroethane	Reflux	9	92	11
15	PW acid	Solvent-free	100	1.5	91	16
16	$Fe(HSO_4)$	Solvent-free	125	0.12	93	15
17	Wet TCT	Solvent-free	110	0.35	91	21
18	$Al(HSO_4)_3$	Solvent-free	125	0.29	90	17

[a]Isolated yield. [b]The reaction was carried out with 4-chlorobenzaldehyde (100mmol), β-naphthol (200 mmol) and PEG-400 (100g) by using TCT (1.37 mol%).

Table 2: Synthesis of 1, 4-substited-14-*H* dibenzo [*a, j*] xanthenes using TCT as a catalyst in the presence of PEG-400 at room temperature.

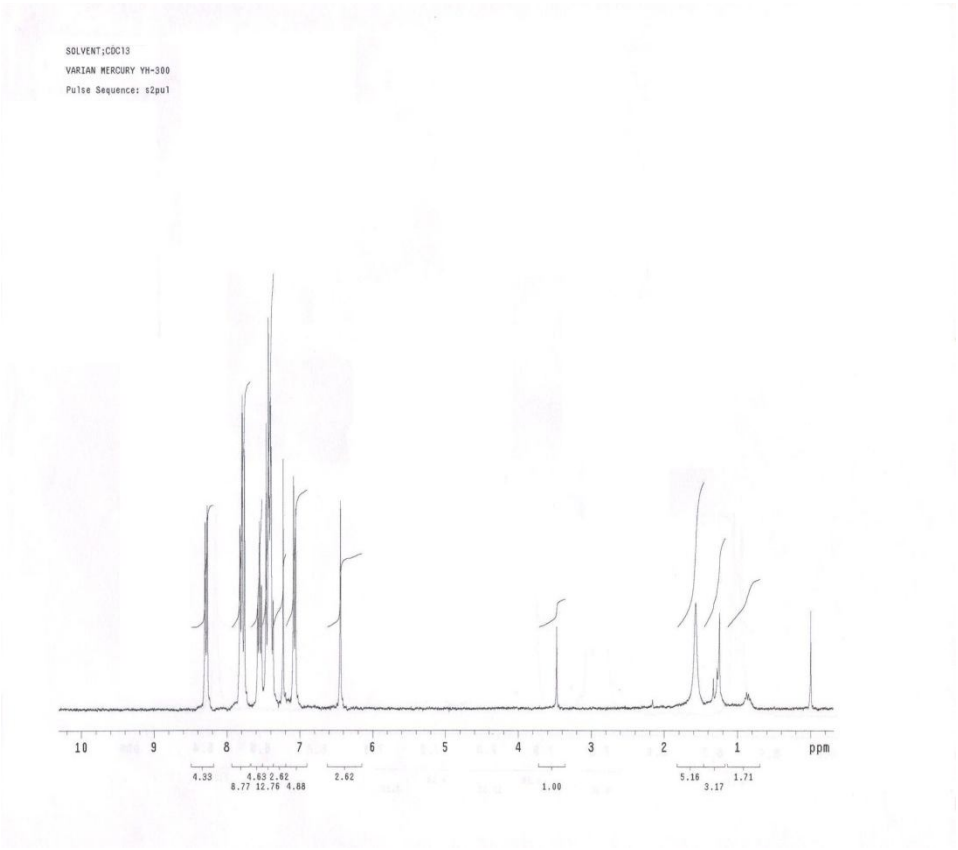
Entry	Aldehyde	Product	Time (h)	Yield (%)[a]	M.P. (^{0}C)
1		3a	1.30	94	287[16]
2		3b	1.45	95	309[16]
3		3c	1.50	92	212[16]
4		3d	1.50	93	258[19]
5		3e	1.35	96	238-40[19]
6		3f	2.00	90	183[16]
7		3g	1.40	87	257-58[38]
8		3h	1.35	89	205[16]
9		3i	1.35	91	230[16]
10		3j	1.25	96	243-45[22]

11		3k	2.30	84	272-74[19]
12		3l	2.30	85	213-14[16]
13		3m	2.25	87	155-57[38]

[a] Yield of pure isolated products.

3. NMR DATA – SPECTRA

3a: 14-(4-Chlorophenyl)-14*H*-dibenzo[*a,j*]xanthene; Faint yellow solid; mp 287^{0}C; IR (KBr): 3069, 1630, 1583, 1244, 817, 807 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 6.44 (s, 1H, C-H), 7.07 (d, 2H, *J* = 8.4 Hz, Ar-H), 7.37-7.82 (m, 12H, Ar-H), 8.28 (d, 2H, *J* = 8.4 Hz, Ar-H); Anal. calcd for $C_{27}H_{17}ClO$: C, 82.56; H, 4.36; Found: C, 82.54; H, 4.39.



3b: 14-(4-Nitrophenyl)-14*H*-dibenzo[*a,j*]xanthene; Yellow solid; mp 309^{0}C; IR (KBr): 3068, 1631, 1594, 1245, 817, 805 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300MHz): δ = 6.52 (s, 1H, C-H), 7.14-7.89 (m, 12H, Ar-H), 8.16 (d, 2H, *J* = 8.5 Hz, Ar-H), 8.50 (d, 2H, *J* = 8.5 Hz, Ar-H); Anal. calcd for $C_{27}H_{17}NO_3$: C, 80.38; H, 4.25; N, 3.27 Found: C, 80.35; H, 4.27; N, 3.29.

3c: 14-(3-Nitrophenyl)-14*H*-dibenzo[*a,j*]xanthene; Yellow solid; mp 212^{0}C; IR (KBr): 3053, 1630, 1583, 1245, 815, 803 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 6.56 (s, 1H, C-H), 7.10-8.70 (m,

16H, Ar-H); Anal. calcd for $C_{27}H_{17}NO_3$: C, 80.38; H, 4.25; N, 3.27; Found: C, 80.39; H, 4.28; N, 3.24.

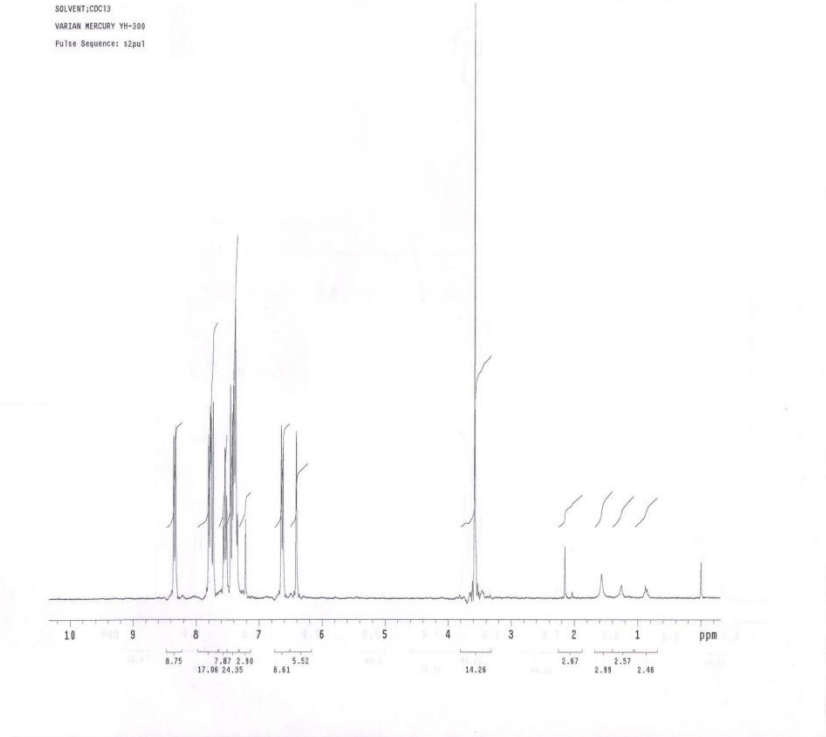
3d: 14-(3-Flurophenyl)-14*H*-dibenzo[*a,j*]xanthene; Faint yellow solid; mp 258^{0}C; IR (KBr): 3058, 1602, 1593, 1247, 810, 754 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 6.80 (s, 1H, C-H), 7.16-8.17 (m, 16H, Ar-H); Anal.calcdfor$C_{27}H_{17}FO$: C, 86.15; H, 4.55; Found: C, 86.15; H, 4.55.

3e: 14-(4-Flurophenyl)-14*H*-dibenzo[*a,j*]xanthene; Faint yellow solid; mp 338-340^{0}c; IR (KBr): 3051, 1605, 1583, 1248, 815, 801 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 6.96 (s, 1H, C-H), 7.40-8.74 (m, 16H, Ar-H); Anal.calcdfor$C_{27}H_{17}FO$: C, 86.15; H, 4.55; Found: C, 86.21; H, 4.58.

3f: 14-Phenyl-14*H*-dibenzo[*a,j*]xanthene; Brown solid; mp 183^{0}C; IR (KBr): 3032, 1619, 1582, 1241, 810, 798 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 6.51 (s, 1H, C-H), 7.02-8.13 (m, 16H, Ar-H); Anal. calcd for $C_{27}H_{18}O$: C, 90.47; H, 5.06; Found: C, 90.45; H, 5.10.

3g: 14-(2-Methoxyphenyl)-14*H*-dibenzo[*a,j*]xanthenes; White solid; mp 257-258^{0}C; IR (KBr): 3028, 1627, 1565, 1259, 845, 746 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.97 (s, 3H, OCH_3), 6.38 (s, 1H, C-H), 6.98 (d, 1H, *J* = 8.6 Hz, Ar-H), 7.20 (d, 1H, *J* = 8.6 Hz, Ar-H), 7.44-7.87 (m, 12H,Ar-H), 7.94 (d, 1H, *J* = 8.6 Hz, Ar-H), 8.33 (s, 1H, Ar-H); Anal. calcd for $C_{28}H_{20}O_2$: C, 86.57; H, 5.19; Found: C, 86.54; H, 5.21.

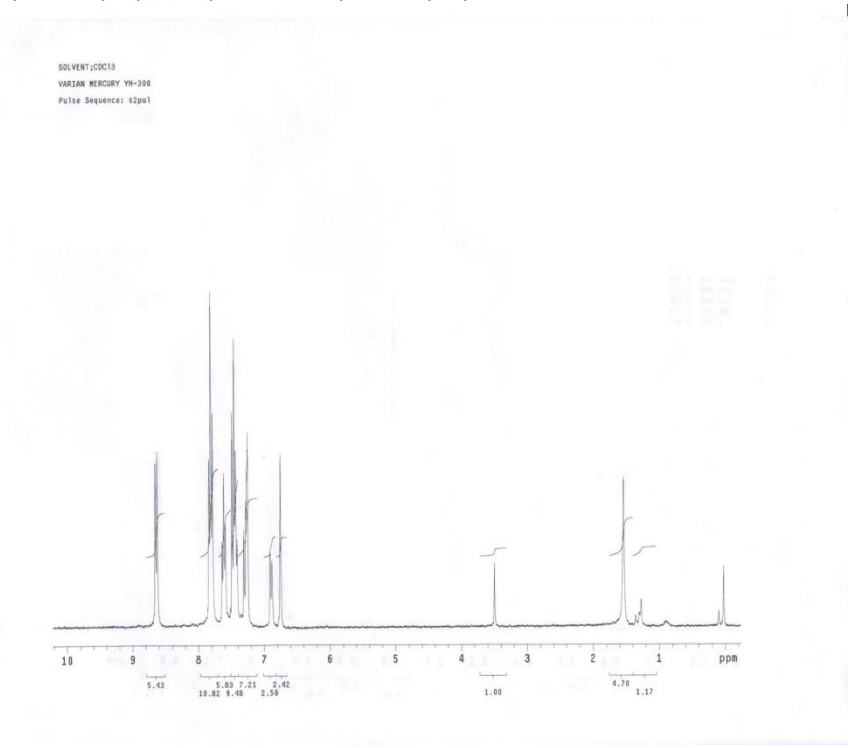
3h: 14-(4-Methoxyphenyl)-14*H*-dibenzo[*a,j*]xanthene; White solid; mp 205^{0}C; IR (KBr): 3039, 1623, 1588, 1257, 815, 736 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.58 (s, 3H, OCH_3), 6.40 (s, 1H, C-H), 6.62 (d, 2H, *J* = 8.4 Hz, Ar-H), 7.34-7.77 (m, 12H,Ar-H), 8.33 (d, 2H, *J* = 8.4 Hz, Ar-H); Anal. calcd for $C_{28}H_{20}O_2$: C, 86.57; H, 5.19; Found: C, 86.54; H, 5.21.



3i: 14-(4-Methylphenyl)-14*H*-dibenzo[*a,j*]xanthene; Brown red solid; mp 230^{0}C; IR (KBr): 3041, 1621, 1240, 818, 735 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.34 (s, 3H, CH_3),6.61 (s, 1H, C-

H), 6.70 (d, 2H, *J* = 8.5 Hz, Ar-H),7.38-7.80 (m, 12H, Ar-H), 8.30 (d, 2H, *J* = 8.5 Hz, Ar-H); Anal. calcd for $C_{28}H_{20}O$: C, 90.29; H, 5.41; Found: C, 90.31; H, 5.44.

3j: 14-(3,4-Dichlorophenyl)-14*H*-dibenzo[*a,j*]xanthene; White solid mp 243-245^{0}C; IR (KBr): 3071, 1635, 1596, 1249, 835, 809 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 6.75 (s, 1H, C-H), 6.91 (d, 1H, *J* = 8.7 Hz Ar-H), 7.25-7.78 (m, 12H, Ar-H), 8.45 (d, 2H, *J* = 8.4 Hz, Ar-H); Anal. calcd for $C_{27}H_{16}Cl_2O$: C, 75.91; H, 3.77; Found: C, 75.90; H, 3.79.



3k: 14- Methyl-14*H*-dibenzo[*a,j*]xanthenes; Brown solid; mp 272-274^{0}c; (KBr): 3049,2910,1248 cm^{-1}; ^{1}H NMR (, $CDCl_3$, 300 MHz): δ = 1.12 (d, 3 H, *J* = 6.2 Hz, CH_3) 5.20 (q, 1H, *J* = 6.2 Hz, C-H), 7.12 -7.40 (m, 12 H, Ar-H). Anal. calcd for $C_{22}H_{16}O$: C, 89.17; H, 5.43. Found: C, 89.13; H, 5.80.

3l: 14-Ethyl-14*H*-dibenzo[*a,j*]xanthene; White brown solid; mp 112-13 °C. IR (KBr): 3047, 2904, 1614, 1223 cm-$^{1.}$ ^{1}H NMR (, $CDCl_3$, 300 MHz): δ = 0.98 (t, 3 H, *J* = 6.2 Hz, CH_3) 1.50 (m, 2H, -CH_2-), 5.06 (t, 1H, *J* = 6.2 Hz, C-H) 7.09-7.97 (m, 12 H, Ar-H). Anal. calcd for $C_{23}H_{18}O$: C, 89.00; H, 5.85. Found: C, 89.14; H, 5.79.

3m: 14-Isopropyl -14*H*-dibenzo[*a,j*]xanthene; White brown solid; mp 155-157 °C. IR (KBr): 3067, 2909, 1616, 1228 cm-$^{1.}$ ^{1}H NMR (, $CDCl_3$, 300 MHz): δ = 0.99 (m, 6 H, *J* = 6.1 Hz, 2CH_3) 1.58 (m, 1H, -CH-), 5.12 (d, 1H, *J* = 6.1 Hz, C-H) 7.06-7.98 (m, 12 H, Ar-H). Anal. calcd for $C_{24}H_{20}O$: C, 88.85.; H, 6.21 Found: C, 89.01; H, 5.99.

4. CONCLUSION

In conclusion, we have developed a simple, clean, efficient and convenient method for the synthesis of 14-substituted 14*H*-benzo [*a, j*] xanthenes using PEG-400 as a green reaction

medium at room temperature. The method reported here is not only simple to operate but also environmentally benign. This approach could make a valuable contribution to the existing process in the field of synthesis of xanthenes.

5. EXPERIMENTAL

5.1 General remarks

Cyanuric chloride, a bright white colored powder and colorless liquid PEG-400 were purchased from Sigma-Aldrich and used without any further purification. Melting points were determined in a capillary Electro-thermal melting point apparatus and are given uncorrected. ^{1}H NMR spectra were recorded using Varian Mercury YH-300MHz spectrometer with TMS as an internal standard. Infrared spectra were taken with a Perkin Elmer 1310 spectrometer. Elemental analysis was recorded on ELEMENTAR (Vario EL, Germany).

5.2. Synthesis of 14-alkyl or aryl dibenzo[a,j]xanthenes (general procedure).

Amixture of aldehyde (5 mmol), β-naphthol (10 mmol), cyanuric chloride (0.5mmol) and PEG-400 (5g) was stirred at room temperature for the specified time (Table 2). The progress of the reaction was monitored by TLC. After completion of the reaction, the resulting suspension was poured onto crushed ice (10g). The products were separated by filtration under suction and recrystallized from hot ethanol to get analytically pure compounds.

6. FUNDING

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