A Facile, Simple and Convenient Method for the Synthesis of 14-Alkyl or Aryl-14-*H*-Dibenzo[*a*,*j*]xanthenes Catalyzed by *p*TSA in Solution and Solvent-Free Conditions

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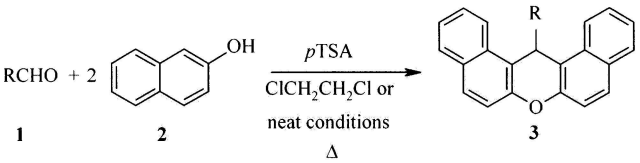
Abstract: An efficient and straightforward procedure for the synthesis of 14-alkyl or aryl-14-*H*-dibenzo[*a*,*j*]xanthenes has been achieved through the one-pot condensation of β-naphthol with alkyl or aryl aldehydes in the presence of *p*-toluene sulfonic acid as catalyst under two conditions: organic solvent and solvent-free media.

Key words: xanthene, one-pot reaction, condensation, aldehyde, β-naphthol, *p*-toluenesulfonic acid, solvent-free, organic solvent

The preparation of xanthenes, especially benzoxanthenes, has received significant attention in previous years because of the broad spectrum of their biological and pharmaceutical properties such as antiviral,[1] antibacterial,[2] and anti-inflammatory[3] activities as well as efficacy in photodynamic therapy[4] and antagonists for the paralyzing action of zoxazolamine.[5] Furthermore, these compounds can be employed as dyes,[6] pH-sensitive fluorescent materials for visualization of biomolecules[7] and utilized in laser technologies.[8] Thus, the synthesis of heterocyclic nucleus currently is of much importance.

Various methods are available for the construction of xanthenes and benzoxanthenes involving the cycloacylation of carbamates,[9] trapping of benzynes by phenols,[10] cyclocondensation reaction between 2-hydroxyaromatic aldehydes and 2-tetralone[11] and intramolecular phenylcarbonyl coupling reaction of benzaldehydes and acetophenones.[12] The synthesis of benzoxanthenes has been achieved by the reaction of aldehydes with β-naphthol by dehydration.[13] Other routes also reported for the synthesis of benzoxanthenes include the reaction of β-naphthol with (a) formamide,[14] (b) carbon monoxide,[15] (c) aldehyde acetals,[13a] and (d) 2-naphthol-1-methanol.[16]

However, these methodologies suffer from one or more disadvantages such as low yield, lack of easy availability/preparation of the starting materials, prolonged reaction time (16 h to 5 d), use of toxic organic solvents, requirement of excess of reagents/catalysts, special apparatus, and harsh reaction conditions. Thus, the need for the development of an alternate route to construct the xanthene derivatives is in high demand. During the course of our recent studies directed towards the development of practical, safe and environmentally friendly procedures for some important transformations,[17] we wish to report an efficient, convenient and facile method for the condensation of aldehydes with β-naphthol to the corresponding benzoxanthenes in the presence of PTSA as catalyst (Scheme 1).



Scheme 1

In an initial study, in order to examine the catalytic activity of different catalysts such as $BiCl_3$, $Bi(NO_3)_3 \cdot 5H_2O$, $Bi(OTf)_3$, $CeCl_3 \cdot 7H_2O$, $ZrCl_4$, $SnCl_2$, $AlCl_3$, $IrCl_3$, $FeCl_3$, CAN and *p*TSA in this condensation reaction, 4-chlorobenzaldehyde was first reacted with **2** in 1,2-dichloroethane (1 mL) for 18 hours under reflux conditions in the presence of catalyst (0.1 equiv). In the course of this study it was found that *p*TSA was the most effective catalyst in terms of yield of the benzoxanthene (93%) while other catalysts formed the product with yields of 0–37%. The solvent effect was also examined by the reaction of 4-chlorobenzaldehyde (1 equiv) with β-naphthol (2 equiv) in the presence of *p*-toluenesulfonic acid (0.1 equiv) in different refluxing solvents (Table 1).

Table 1 Solvent Effect on the Reaction of 4-Chlorobenzaldehyde and β-Naphthol Catalyzed by *p*TSA[a]

Entry	Solvent	Time (h)	Yield (%)[b]
1	$ClCH_2CH_2Cl$	18	93
2	MeCN	18	35
3	DMF	18	nil
4	MeOH	18	81
5	EtOH	18	65
6	$CHCl_3$	18	60
7	1,4-Dioxane	18	80

[a] 10 mol%.
[b] Isolated yield.

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As shown in Table 1, the product was obtained after 18 hours in 1,2-dichloroethane in excellent yield (93%). The generality of this condensation reaction proceeded effectively under these conditions with β-naphthol and a wide range of aliphatic and aromatic aldehydes (Table 2, method A).

We therefore undertook an optimization of the reaction conditions to improve the reaction time. Surprisingly it was found that aldehyde **1** (1.0 mmol) was very rapidly (<6 min) converted into benzoxanthene **3** when heated at 125 °C with **2** (2.0 mmol) in the presence of only 2 mol% of *p*TSA under solvent-free conditions (Scheme 1). The experimental procedure for this reaction is remarkably simple and requires no toxic organic solvents or inert atmosphere. However, the synthesis could not be achieved in the absence of the catalyst.

We examined the reaction using various aliphatic and aromatic aldehydes under solvent-free conditions and the results are summarized in Table 2 (method B).

Table 2 Synthesis of 14-Alkyl- or Aryl-14-*H*-dibenzo[*a*,*j*]xanthenes in the Presence of a Catalytic Amount of *p*TSA[a]

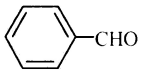
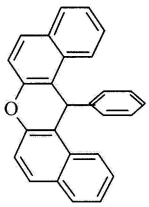
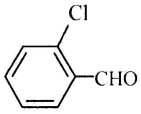
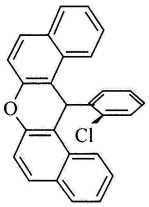
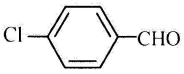
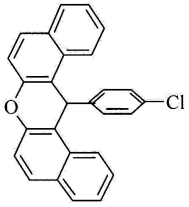
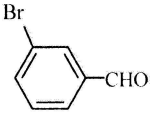
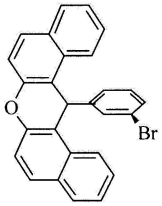
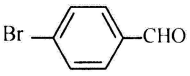
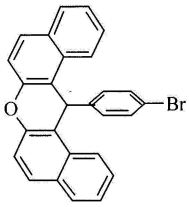
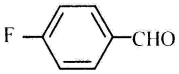
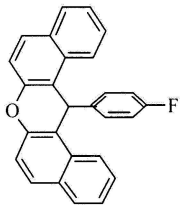
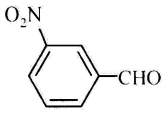
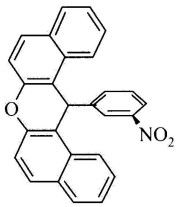
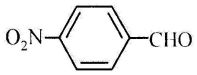
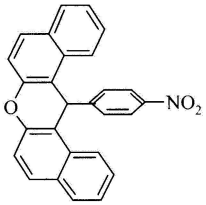
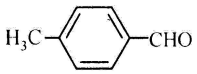
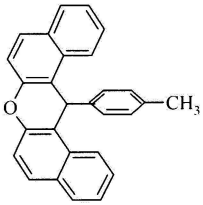
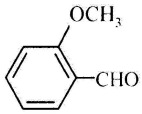
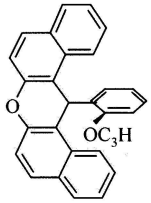
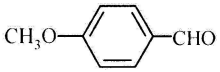
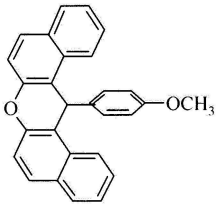
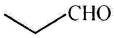
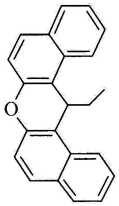
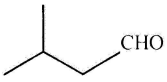
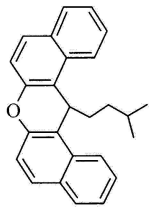
Entry	Aldehyde	Product[b]	Method A		Method B		Mp (°C)
			Time (h)	Yield (%)[c]	Time (h)	Yield (%)[c]	
1			20	91	4	89	185[13d]
2			21	87	2.5	88	215
3			18	93	2.5	95	289
4			21	90	2.5	91	192
5			15	95	2.5	96	297[13d]
6			18	92	3	90	239

Table 2 Synthesis of 14-Alkyl- or Aryl-14-*H*-dibenzo[*a*,*j*]xanthenes in the Presence of a Catalytic Amount of *p*TSA[a] (continued)

Entry	Aldehyde	Product[b]	Method A		Method B		Mp (°C)
			Time (h)	Yield (%)[c]	Time (h)	Yield (%)[c]	
7			24	89	2.5	90	211
8			20	93	2.5	90	310[13d]
9			18	90	3	92	229[13d]
10			24	88	6	82	260
11			22	90	6	80	204
12			30	85	5	81	152[13d]
13			30	88	5	85	113

[a] Method A: reaction carried out with 10 mol% of *p*TSA in 1,2-dichloroethane under reflux conditions. Method B: reactions were carried out with 2 mol% of *p*TSA under solvent-free conditions at 125 °C.
[b] The products were characterized by ^{1}H NMR, ^{13}C NMR, IR and comparison with reported data.[18]
[c] Isolated yields.

Several functionalities present in the aryl aldehydes such as halogen, methoxy and nitro group were tolerated. In all the cases the corresponding benzoxanthenes were obtained in good to excellent yields. These results were also obtained in the case of the aliphatic aldehydes (Table 2, entries 12, 13).

In summary, a novel and highly efficient methodology for the synthesis of 14-alkyl- or -aryl-14-*H*-dibenzo[*a*,*j*]xanthenes by condensation reaction of aldehydes and β-naphthol in the presence of catalytic amounts of *p*TSA under organic solvent (method A) and solvent-free conditions (method B) was reported. In addition to the efficiency and simplicity provided by method B, this protocol describes a very fast, 'green' and low cost procedure for the synthesis of these products.

Typical Experimental Procedure (Method A)
A mixture of aldehyde (1 mmol), β-naphthol (2 mmol) and *p*TSA (0.1 mmol) in 1,2-dichloroethane was stirred at reflux for the appropriate time according to Table 2. The progress of the reaction was monitored by thin layer chromatography. After completion of the reactions, the organic solvent was evaporated and a mixture of EtOH–H_2O (1:3) was added to it. The suspension was stirred for 5 min and the precipitate filtered. The crude products were purified by recrystallization from EtOH.

Typical Experimental Procedure (Method B)
To a mixture of aldehyde (1 mmol) and β-naphthol (2 mmol), *p*TSA (0.02 mmol) was added. The reaction mixture stirred magnetically at 125 °C for the appropriate time as shown in Table 2. The reaction was followed by TLC. When the reaction was completed, the mixture was washed with EtOH–H_2O (1:3). The crude products were purified by recrystallization from EtOH.

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(18) **Selected Characterization Data of: 14-(3-Nitrophenyl)-14-*H*-dibenzo[*a*,*j*]xanthene (Table 2, Entry 7)**: yellow solid; mp 211 °C. IR (KBr): 3040, 1612, 1584, 1516, 1248, 812, 803 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 6.65 (s, 1 H), 7.15–8.6 (m, 17 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 38.1, 116.3, 118.5, 122.1, 122.4, 123.1, 125.0, 127.7, 129.5, 129.9, 130, 131.5, 131.8, 134.7, 147.4, 148.6, 149.2. Anal. Calcd for $C_{27}H_{17}NO_3$: C, 80.38; H, 4.25; N, 3.47. Found: C, 80.27; H, 4.08; N, 3.56.
14-(4-Methoxyphenyl) -14-*H*-dibenzo[*a*,*j*]xanthene (Table 2, Entry 11): yellow solid; mp 204 °C. IR (KBr): 3040, 2912, 1616, 1580, 1248, 823, 806 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 3.67 (s, 3 H), 6.52 (s, 1 H), 6.71 (d, *J* = 9.5 Hz, 2 H), 7.38–7.95 (m, 14 H), 8.43 (d, *J* = 9.5 Hz, 2 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 37.5, 53.9, 114.3, 117.9, 118.4, 123.1, 124.6, 127.2, 129.1, 129.2, 131.5, 133.7, 137.8, 149.1, 158.3. Anal. Calcd for $C_{28}H_{20}O_2$: C, 86.57; H, 5.19. Found: C, 86.32; H, 5.31.