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# pTSA-catalyzed one-pot synthesis of 12-aryl-8,9,10,12-tetrahydrobenzo[*a*]xanthen-11-ones in ionic liquid and neat conditions

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ABSTRACT

Multi-component condensation of β-naphthol, aromatic aldehydes, and cyclic 1,3-dicarbonyl compounds catalyzed by *p*-toluenesulfonic acid has been accomplished for the synthesis of a series of 12-aryl-8,9,10,12-tetrahydrobenzo[*a*]xanthen-11-ones in ionic liquid([bmim]$BF_4$) and in solvent-free media. High yields, ease of recovery, and reusable reaction medium (ionic liquid) with consistent activity makes this protocol efficient and environmentally benign.



## 1. Introduction

Xanthenes and benzoxanthenes are important heterocycles that are known to possess multiple biological activities. Although not widely found in nature, xanthenes and compounds based on these core templates exhibit a broad spectrum of pharmaceutical activities such as *anti*-bacterial,[1] *anti*-inflammatory,[2] and *anti*-viral.[3] These structural motifs have also found a niche as antagonists for paralyzing the action of zoxazolamine[4] and demonstrate efficacy in photodynamic therapy.[5] In addition, these compounds have been employed as dyes,[6]and pH-sensitive fluorescent materials for visualization of biomolecular assemblies[7] and utilized in laser technologies.[8] Thus a broad utility range has made xanthenes prime synthetic candidates thereby accentuating the need to develop newer synthetic routes for scaffold manipulation of xanthene derivatives. The synthesis of tetrahydrobenzo[*a*]xanthen-11-ones has been reported in the presence of strontium triflate[9] and $NaHSO_4{\cdot}SiO_2$ under reflux in halogenated solvents for long hours.[10] In this context it can undoubtedly be stated that solvent-free neat reactions and the use of ionic liquids as 'green' recyclable substitutes to the traditional volatile organic solvents[11] have experienced an impetus in recent years. Their negligible vapor pressure makes them easily confinable and also enables an easy recyclability. Moreover, the solvophobic properties of ionic liquids are able to generate an internal pressure and promote the association of reactants in the solvent cavity during the activation process.

Thus ionic liquids are well suited as reaction media for MCRs (multi-component reactions) in which the entropy of the reaction is decreased in the transition state.

In view of our ongoing efforts to explore newer reactions for synthesis of heterocyclic compounds,[12] we decided to investigate the possibility of synthesizing tetrahydrobenzo[*a*]xanthen-11-one derivatives by one-pot three-component condensation reaction strategy of β-naphthol with aldehydes and cyclic 1,3-dicarbonyl compounds in ionic liquids as well as under neat conditions.

## 2. Results and discussion

In this Letter, we report an efficient and environmentally benign protocol for the synthesis of 12-aryl-8,9,10,12-tetrahydrobenzo[*a*]xanthen-11-one derivatives by multi-component condensation of β-naphthol, aromatic aldehydes, and cyclic 1,3-dicarbonyl compounds catalyzed by pTSA in ionic liquid ([bmim]$BF_4$) and also under solvent-free neat conditions. The products were obtained in high yields by a simple work-up. The condensation of benzaldehyde (1.0 mmol), β-naphthol (1.0 mmol), and 5,5-dimethylcyclohexane-1,3-dione (1.2 mmol) was attempted in different ionic liquids at room temperature and also under heating. Only 28% of the desired 12-phenyl-8,9,10,12-tetrahydrobenzo[*a*]xanthen-11-one (**1a**) was obtained after heating the reaction mixture for 14 h at 80 °C in [bmim]$BF_4$ in the absence of a catalyst. The reaction was then attempted under similar conditions in the presence of different acids. The reactions carried out in the presence of $H_2SO_4$, HCl, and $CH_3COOH$ were sluggish and incom-

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plete even after 10 h. The yield of the product improved remarkably to 90% after heating the components at 80 °C for 3 h in the presence of catalytic amount of pTSA. Subsequently, the condensation was attempted in different ionic liquids but the efficiency and the yield of the reaction in [bmim]$BF_4$ were higher than those in other ionic liquids thereby making [bmim]$BF_4$ the most suitable reaction medium for successive reactions.

The application of this protocol was extended to a variety of aromatic aldehydes. The reactions proceeded smoothly with different aldehydes substituted with electron-donating/electron-withdrawing groups giving excellent yields (Scheme 1). Interestingly halo-substituted aromatic aldehydes required shorter reaction times than their electron-rich counterparts. These results are compiled in Table 1 (entries 1–12, method A).

In order to broaden the scope of this protocol further, we decided to explore the cyclocondensation reaction of cyclohexane-1,3-dione with aldehydes and β-naphthol. The reaction of benzaldehyde (1.0 mmol), β-naphthol (1.0 mmol), and cyclohexane-1,3-dione (1.2 mmol) in [bmim]$BF_4$ using pTSA as the catalyst under similar conditions yielded 88% of tetrahydrobenzo[*a*]xanthene-11-one derivative (1 m) after 3.5 h. Other substituted benzaldehydes also underwent successful condensation with β-naphthol and cyclohexane-1,3-dione (Table 1, entries 13–17).

It is obvious from the above observations that pTSA in [bmim]$BF_4$ is an efficient system for the synthesis of tetrahydrobenzo[*a*]xanthen-11-ones. However, we decided to investigate the reaction further under solvent-free neat conditions and thereby optimize the reaction conditions, if successful. Therefore, 4-chlorobenzaldehde, β-naphthol, and dimedone were mixed thoroughly and heated in a round-bottomed flask using varying amounts of pTSA at different temperatures. It was observed that the reaction was complete in 35 min by heating the mixture in an oil bath maintained at 120 °C in the presence of only 2 mol % of pTSA yielding 86% of pure **1b** by a simple work-up. The reaction did not proceed successfully in the absence of the catalyst. The reaction procedure is remarkably simple and requires no solvent media. Other substituted aromatic aldehydes also underwent condensation under these conditions and the corresponding xanthene derivatives were obtained in high yields (method B, entries 1–12). Also, on replacing dimedone with cyclohexane-1,3-dione, the reaction reached successful completion under neat conditions. A comparison of the results obtained is drawn (Table 1, method B, entries 13–17). Though comparative yields were obtained by both methods, the reactions carried out under neat conditions required much shorter times for completion. A plausible mechanism for the formation of 12-aryl-8,9,10,12-tetrahydrobenzo[*a*]xanthen-11-one derivatives (**1a–q**) in the presence of pTSA is proposed in Scheme 2.

**Table 1**
Synthesis of 12-aryl-8,9,10,12-tetrahydrobenzo[*a*]xanthen-11-one derivatives by condensation of aldehydes, β-naphthol, and 5,5-dimethylcyclohexane-1,3-dione/cyclohexane-1,3-dione using pTSA as the catalyst

| Entry | R | Product | Method A | | Method B | |
|---|---|---|---|---|---|---|
| | | | Time (h) | Yield (%) | Time (min) | Yield (%) |
| 1 | $C_6H_5$ | **1a** | 3.0 | 90 | 45 | 88 |
| 2 | 4-$ClC_6H_4$ | **1b** | 2.0 | 85 | 35 | 86 |
| 3 | 4-$BrC_6H_4$ | **1c** | 2.0 | 86 | 35 | 82 |
| 4 | 4-$CH_3C_6H_4$ | **1d** | 3.0 | 90 | 40 | 88 |
| 5 | 2,4-$Cl_2C_6H_3$ | **1e** | 2.0 | 95 | 35 | 90 |
| 6 | 2-$BrC_6H_4$ | **1f** | 2.5 | 91 | 40 | 92 |
| 7 | 4-$CH_3OC_6H_4$ | **1g** | 3.5 | 83 | 45 | 85 |
| 8 | 2-Naphthyl | **1h** | 3.0 | 90 | 45 | 90 |
| 9 | 4-$HOC_6H_4$ | **1i** | 3.5 | 88 | 45 | 86 |
| 10 | 4-$FC_6H_4$ | **1j** | 2.5 | 85 | 40 | 82 |
| 11 | 3-$CF_3C_6H_4$ | **1k** | 2.5 | 84 | 40 | 84 |
| 12 | 3-$BrC_6H_4$ | **1l** | 2.0 | 91 | 40 | 89 |
| 13 | $C_6H_5$ | **1m** | 3.5 | 88 | 40 | 89 |
| 14 | 4-$ClC_6H_4$ | **1n** | 2.5 | 84 | 40 | 80 |
| 15 | 2-$BrC_6H_4$ | **1o** | 3.0 | 90 | 40 | 86 |
| 16 | 3-$ClC_6H_4$ | **1p** | 2.5 | 89 | 40 | 90 |
| 17 | 4-$NO_2C_6H_4$ | **1q** | 2.5 | 92 | 40 | 90 |

## 3. Conclusion

In conclusion, we have described an efficient and environmentally benign method for the preparation of 12-aryl-8,9,10,12-tetrahydrobenzo[*a*]xanthen-11-ones. This multi-component cyclocondensation reaction is efficiently catalyzed by pTSA in ionic liquid at 80 °C and under neat conditions at 120 °C. Operational simplicity, mild reaction conditions, enhanced rates, and high isolated yields of the pure products are significant advantages of the protocol presented here.

## 4. Experimental

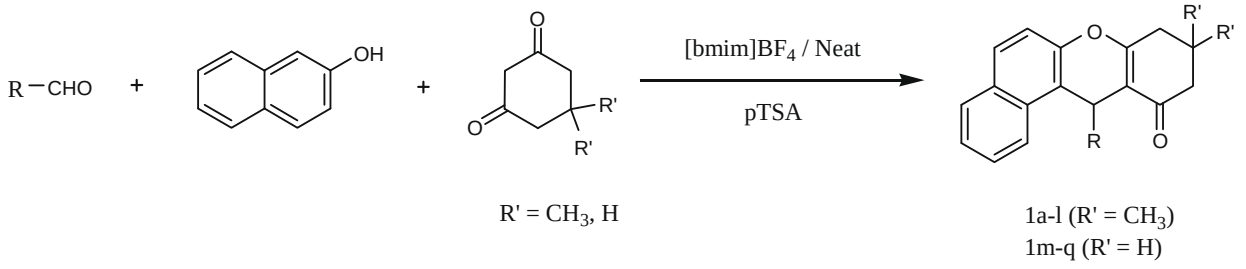
### 4.1. General

The products were characterized by IR spectra, $^1H$ NMR, $^{13}C$ NMR, and FAB mass analyses. IR spectra were recorded on Perkin–Elmer FT-IR-1710 instrument. $^1H$ and $^{13}C$ NMR spectra were recorded on Bruker Advance Spectrospin 300 MHz and 400 MHz using TMS as the internal standard. FAB mass spectra were recorded on Jeol SX 102/Da-600 mass spectrometer using Argon/ Xenon as the FAB gas.

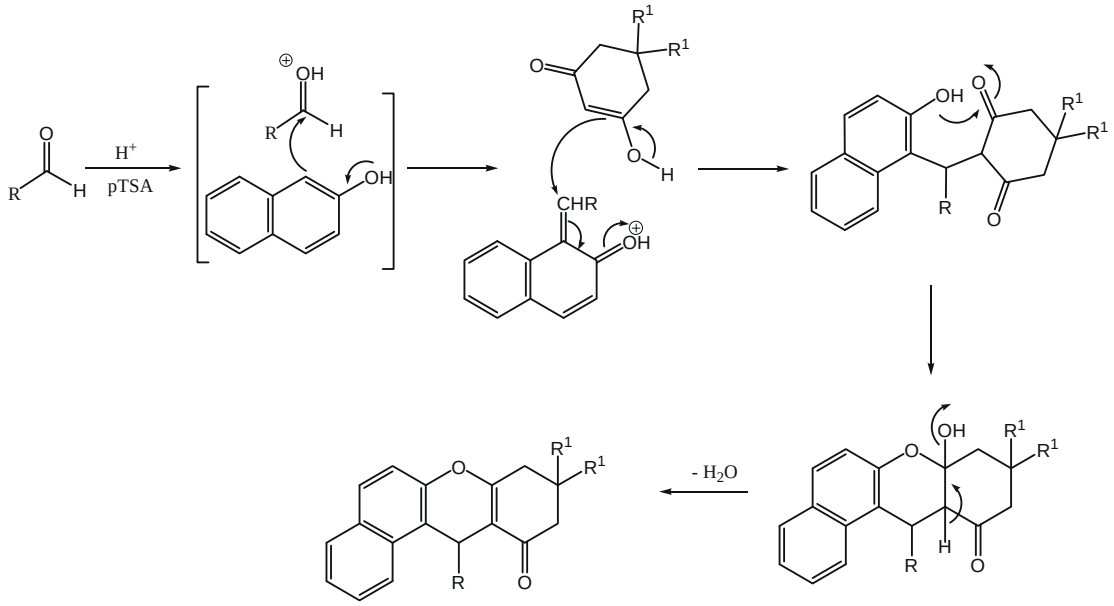
### 4.2. General procedure for the synthesis of 12-aryl-8,9,10,12-tetrahydrobenzo[*a*]xanthen-11-one derivative (1a–q)

#### 4.2.1. Method A

Aldehyde (1.0 mmol), β-naphthol (1.0 mmol), 5,5-dimethyl-1,3-cyclohexanedione/1,3-cyclohexanedione (1.2 mmol), and pTSA (0.1 mmol) were taken in a 10-mL round-bottomed flask containing 0.5 mL of [bmim]$BF_4$. The mixture was stirred at 80 °C for an appropriate time as mentioned in Table 1. After completion of the reaction as monitored by TLC, the mixture




**Scheme 1.**




**Scheme 2.**

was allowed to cool to room temperature and quenched with water (~5 mL). The precipitate formed was collected by filtration at pump, washed with water, and dried. The filtrate was concentrated under reduced pressure and dried at 100 °C to recover the ionic liquid for subsequent use. The crude product was recrystallized from ethanol to yield pure xanthen-11-one derivative.

### 4.2.2. Method B

Aldehyde (1.0 mmol), β-naphthol (1.0 mmol), and 5,5-dimethyl-1,3-cyclohexanedione/1,3-cyclohexanedione (1.2 mmol) were mixed thoroughly and placed in a 10-mL round-bottomed flask. pTSA (0.02 mmol) was added to the mixture and the mixture was heated in an oil bath maintained at 120 °C for appropriate time as given in Table 1. The reaction mixture was then cooled to room temperature and quenched with water (~5 mL). The solid mass obtained was washed with EtOH–$H_2O$ (1:1). The solid product obtained was filtered and recrystallized from ethanol to yield pure xanthen-11-one derivative.

## 4.3. Spectral data of some representative products are given below

*Compound* ***1c***: $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.89 (d, $J$ = 8.3 Hz, 1H), 7.76–7.80 (m, 2H), 7.38–7.45 (m, 2H), 7.26–7.33 (m,3H), 7.20–7.23 (m, 2H), 5.66 (s, 1H), 2.56 (s, 2H), 2.31 (d, $J$ = 16.3 Hz, 1H), 2.24 (d, $J$ = 16.3 Hz, 1H), 1.12 (s, 3H), 0.96 (s, 3H). $^{13}$C NMR (300 MHz, $CDCl_3$): $\delta$ = 196.8, 164.0, 147.7, 143.7, 131.5, 131.3, 131.2, 130.1, 129.1, 128.5, 127.1, 125.0, 123.4, 120.1, 117.0, 116.9, 113.7, 50.8, 41.4, 34.2, 32.2, 29.3, 27.1. IR $\nu_{max}$ (KBr): 2955, 1652, 1596, 1373, 1228, 1185. MS (FAB): $m/z$ = 433, 435[M+2].

*Compound* ***1d***: $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 8.0 (d, $J$ = 8.4 Hz, 1H), 7.33–7.77 (m, 2H), 7.40–7.44 (m, 1H), 7.32–7.37 (m, 2H), 7.20–7.30 (m, 2H), 6.96 (d, $J$ = 8.0 Hz, 2H), 5.66 (s, 1H), 2.54 (s, 2H), 2.30 (d, $J$ = 16.2 Hz, 1H), 2.23 (d, $J$ = 16.2 Hz, 1H), 2.19 (s, 3H), 1.10 (s, 3H), 0.98 (s, 3H). $^{13}$C NMR (300 MHz, $CDCl_3$): $\delta$ = 196.8, 163.7, 147.7, 141.8, 135.6, 131.5, 131.4, 128.9, 128.6, 128.3, 128.2, 126.9, 124.8, 123.6, 117.9, 117.0,114.4, 50.9, 41.4, 34.2, 32.2, 29.2, 27.2, 20.9. IR $\nu_{max}$ (KBr): 2950, 1649, 1597, 1372, 1228, 1185. MS (FAB): $m/z$ = 368.

*Compound* ***1o***: $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 8.28 (d, $J$ = 8.4 Hz, 1H), 7.72–7.76 (m, 2H), 7.34–7.50 (m, 3H), 7.17–7.30 (m, 2H), 7.0–7.1 (m, 1H), 6.89–7.0 (m, 1H), 5.97 (s, 1H), 2.53–2.83 (m, 2H), 2.23–2.46 (m, 2H), 1.93–2.16 (m, 2H). $^{13}$C NMR (300 MHz, $CDCl_3$): $\delta$ = 196.8, 165.7, 147.5, 144.1, 133.3, 131.8, 131.7, 131.3, 129.1, 128.3, 127.8, 127.6, 127.0, 124.9, 123.4, 117.8, 115.0, 37.1, 35.3, 27.8, 20.3. IR $\nu_{max}$ (KBr): 2957, 1652, 1595, 1371, 1227, 1189. MS (FAB): $m/z$ = 405, 407 [M+2].

*Compound* ***1p***: $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 7.89 (d, $J$ = 8.1 Hz, 1H), 7.76–7.79 (m, 2H), 7.23–7.46 (m, 5H), 6.90–7.17 (m, 2H), 5.71 (s, 1H), 2.60–2.77 (m, 2H), 2.22–2.52 (m, 2H), 1.90–2.12 (m, 2H). $^{13}$C NMR (300 MHz, $CDCl_3$): $\delta$ = 196.9, 165.8, 147.8, 146.9, 134.1, 131.5, 131.2, 129.4, 129.1, 128.5, 128.4, 127.1, 126.8, 125.0, 123.4, 117.0, 116.8, 114.9, 36.9, 34.4, 27.7, 20.2. IR $\nu_{max}$ (KBr): 2952, 1649, 1594, 1375, 1225, 1189. MS (FAB): $m/z$ = 361, 363 [M+2].

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