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# Thiamine hydrochloride as a promoter for the efficient and green synthesis of 12-aryl-8,9,10,12 tetrahydrobenzoxanthene-11-one derivatives in aqueous micellar medium

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Abstract:

Environmentally benign, three-component, one-pot integrated chemical process has been developed for the synthesis of 12-aryl-8,9,10,12-tetrahydrobenzoxanthene-11-one by nucleophilic addition reaction between aldehyde and β-naphthol followed by Michael addition of dimedone, catalyzed by thiamine hydrochloride in aqueous micellar medium with excellent yield. Simple reaction conditions, no requirement of chromatographic separation, short reaction time, ease of isolation, use of inexpensive, easily recoverable and reusable catalyst makes this protocol very interesting from an economic and environmental perspective.

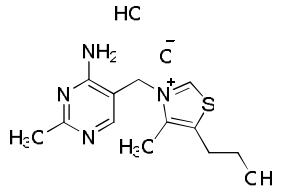
**Keywords:** Benzoxanthenone, Michael addition, nucleophilic addition, Environmentally benign, aqueous micellar medium.

The rapid assembly of molecular diversity is an important aim of synthetic organic chemistry and one of the key paradigms of modern drug discovery. One of the way to cope with this challenge, involves the development of multicomponent reactions (MCRs),[1] in which three or more reactants are combined together in a single reaction flask, incorporating most of the atoms contained in the starting materials, to generate a product. In addition to the intrinsic atom-economy and selectivity underlying such reactions, simpler procedures and equipment, time and energy savings, as well as environmental friendliness[2] have all led to a sizable effort to design and implement MCRs in both academia and industry.[3] As a one-pot reaction, MCRs generally afford good yields and are fundamentally different from two-component reactions in several aspects[4] and permitted rapid access to combinatorial libraries

of organic molecules for efficient structure-identification and optimization, in drug discovery.[5]

Xanthenes and benzoxanthenes exhibit various pharmacological activities and are useful as antibacterial[6] anti-inflammatory[7] and antiviral agents.[8] They are useful antagonists for the paralyzing action of zoxazolamine[9] and also in photodynamic therapy.[10] These compounds were discovered to be pH-sensitive fluorescent materials for visualization of biomolecular assemblies. They can also be utilized as dyes[11] and in laser technologies.[12] The well known dyes having xanthene nucleus are Rhodamine B and Rhodamine 6G.Therefore synthesis of xanthenes has gained prominence in synthetic organic as well as medicinal chemistry.

On the past decade, various methods have been developed for the synthesis of tetrahydrobenzo(a)xanthenes-11-ones. Generally they are synthesized by the three-component condensation of cyclic 1,3-diketone with an aldehyde and *β*-naphthol, which entails the use of PTSA in ionic liquid,[13] perchloric acid adsorbed on silica gel,[14] tetrabutyl ammonium fluoride,[15] dodecatungstophosphoric acid,[16] indium chloride and phosphorus pentaoxide,[17] strontium triflate,[18] $NaHSO_4.SiO_2$,[19] cyanuric chloride,[20] iodine,[21] $Zr(HSO_4)$,[22] silica sulfuric acid,[23] proline triflate[24] in water and TTAB[24b] in water. Although, a number of modified methods, under improved conditions have been reported, many of them suffer from one or more drawbacks, such as unsatisfactory yields, very high temperature, long reaction time and use of toxic organic solvents and catalysts. Hence, it is necessary to develop, an efficient and convenient method to construct these important biologically active heterocyclic compounds. It is well known that thiamine hydrochloride ($VB_1$) is a cheap non-flammable and non-toxic reagent, containing a pyrimidine ring and a thiazole ring linked by a methylene bridge (Fig 1).

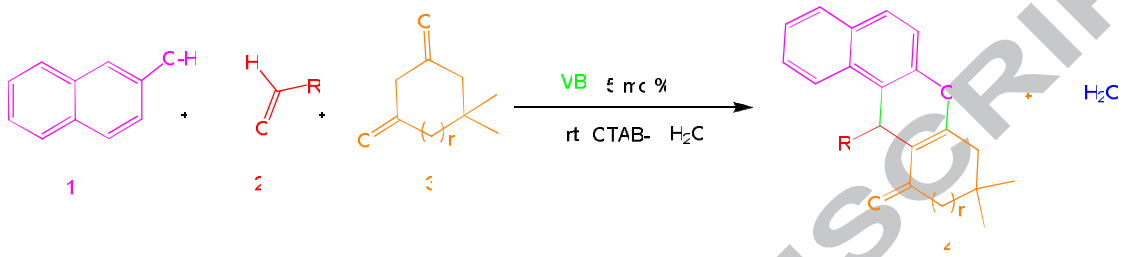



Thiamine hydrochloride (VB1)

Fig 1

$VB_1$ analogs a powerful catalysts have been applied in various organic transformations for carbon-carbon and carbon-heteroatom bond formation reactions.[25] Recently several $VB_1$ catalyzed reactions for the synthesis of heterocyclic compounds such

as pyrimidinones[26] and 1,2-dihydro-naphth-(1,2-e)(1,3)-oxazine-3-one,[27] 1,4-dihydropyridines,[28a] benzo[4,5]imidazo [1,2-a]pyrimidine and [1,2,4]triazolo[1,5-a] pyrimidine[28b] have been reported. We had the opportunity to explore for the first time its catalytic activity towards the synthesis of 12-aryl-8,9,10,12-tetrahydrobenzo(a)xanthenes-11-one derivatives.




**Scheme 1**

From the ecofriendly-point of view, it is of considerable interest to perform organic reactions in water because it is abundant in nature, has virtually no cost, and is safest among available solvents, thus leading to environmentally benign chemical processes.[29] But the basic problem in performing reaction in aqueous medium is that many organic compounds are hydrophobic and are insoluble in water. To overcome this problem is the introduction of aqueous surfactant solutions in the form of micelles[30] as the reaction medium. Considering the significance of surfactants[31-36] and in continuation of our research work[37-39] to develop new and convenient synthetic protocols for the construction of bioactive heterocycles, we targeted to synthesize 12-aryl-8,9,10,12-tetrahydrobenzo[a]xanthen-11-ones using hexadecyltrimethylammonium bromide (CTAB) in aqueous micellar form. The solubilization of water-insoluble reactants and products inside the micelles results not only in high concentration within the small volume, but also in different orientations of the soluble molecules that influence the reaction mechanism, resulting in remarkable differences in reaction rate and selectivity that would be observed in a homogeneous system.

In our initial study, reaction of 4-chlorobenzaldehyde, β-naphthol and dimedone in water was considered as a standard model reaction[40] (Scheme 1). During this investigation, efforts were mainly focused on a variety of surfactants as well as catalyst molar concentration. In this regard, different cationic surfactants such as cetyltrimethylammonium bromide (CTAB), methyltriphenylphosphonium bromide (MTPPB) and cetylpyridinium chloride (CPC) as well as ananionic surfactant, sodium dodecyl sulfate (SDS), were utilized

at ambient temperature. From these preliminary studies, it was observed that the anionic surfactant SDS and cationic surfactants CPC and MTPPB gave the desired product found in low yields, i.e., 57%, 32% and 59% respectively (Table 1, entries 1–3). In contrast, the cationic surfactant CTAB accelerated the model reaction to afford the desired product in good yield (Table 1, entry 4). From this, it was concluded that cationic surfactants, particularly quaternaryammonium bromide (CTAB) where the counter ion is bromide are far superior to other surfactants for efficient catalysis.

**Table 1** Screening of surfactants[a]:

| Entry | Surfactant | Temperature (°C) | Time(hour) | yield[b](%) |
|---|---|---|---|---|
| **1** | SDS | RT[c] | 4.30 | 52 |
| **2** | CPC | RT[c] | 4.0 | 30 |
| **3** | MTPPB | RT[c] | 4.0 | 53 |
| **4** | TEAB | RT[c] | 4.0 | 40 |
| **5** | CTAB | RT[c] | 3.30 | 76 |

[a]reaction conditions**:** β-naphthol **1** (1 mmol), 4-chlorobenzaldehyde **2** (1 mmol), dimedone **3** (1mmol), surfactant (10 mol %), in water (10 ml).
[b]isolated yields; [c]room temperature (RT) was 45 °C.

Encouraged by these results we further investigated the effect of catalyst on the reaction. We found that there is significant reduction in time along with excellent increment in yield on using thiamine hydrochloride as a catalyst in aqueous micellar system. We performed the reaction using different molar concentration of catalyst (Table 2) carefully studied its effect on isolated yield (Fig.2) and found that on using 3, 5, 10 mol% of $VB_1$, the isolated yield were 88%, 92%, 92% respectively . Further increase in catalyst concentration did not lead to significant enhancement in the reaction yield, therefore we decided to use only 5 mol% of the catalyst for the best result.

**Table 2** Optimization of catalyst

| Entry | Catalyst (mol%) | Time(min) | yield of Product[b](%) |
|---|---|---|---|
| **1** | 0 | 210 | 76 |
| **2** | 3 | 46 | 88 |
| **3**[c] | 5 | 25 | 92, 90, 87, 83 |
| **4** | 10 | 25 | 92 |

Conditions: 4-Cl-Benzaldehyde (1 mmol), dimedone (1mmol) and β- naphthol(1 mmol), water(10ml)-CTAB(10mol%), 45°C.
[a]isolated yields.
[b]catalyst was used three times.

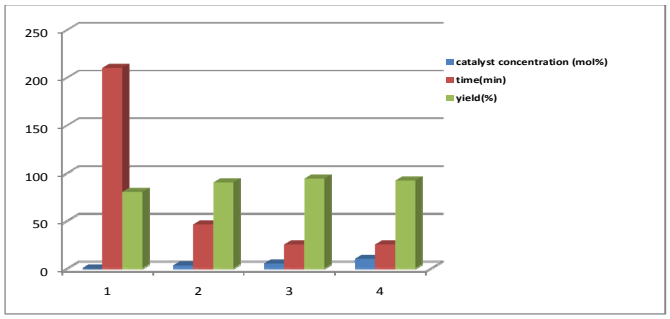



**Fig. 2** Graphical presentation of effect of catalyst concentration on reaction

From the comparable study of the previously reported work on the synthesis of 12-aryl-8,9,10,12-tetrahydrobenzo(a)xanthenes-11-one derivatives and our work (Table 3), we can say that thiamine hydrochloride in aqueous micellar system is an excellent catalyst for reducing the time and enhancing the yield.

To extend the scope of the reaction and to generalize this method, a variety of structurally diverse non-aromatic/ aromatic aldehydes, 5,5-dimethyl-1,3-cyclohexanedione / 5,5-dimethylcyclopentane-1,3-dione, and *β*-naphthol were examined, and the results are summarized in Table 1. Various non aromatic and aromatic aldehydes containing electron-withdrawing and electron-donating substituent at ortho, meta or para-positions were smoothly converted to their corresponding tetrahydroxanthenones in high to excellent yields. To further expand the scope of the present method, the replacement of 5,5-dimethyl-1,3-cyclohexanedione with 5,5-dimethylcyclopentane-1,3-dione was examined. To our delight, under the same optimized conditions, the reactions proceeded steadily to afford a series of xanthene-based compounds in good yields. We have also tried to make benzoxanthen-11-ones using α-naphthol or other phenols instead of *β*-naphthol, it was found that under the same conditions, when *β*-naphthol was replaced by other phenols/ α-naphthol, either no product was obtained or product formation took place with very poor yield. Identity of the synthesized products was confirmed by comparing the physical and spectral data (IR & $^{1}$H NMR) with those of the reported compounds.[14-24]

**Table 3:** Comparison of previously reported work with our work for the synthesis of 12-aryl-8,9,10,12-tetrahydrobenzo(a)xanthenes-11-one derivatives

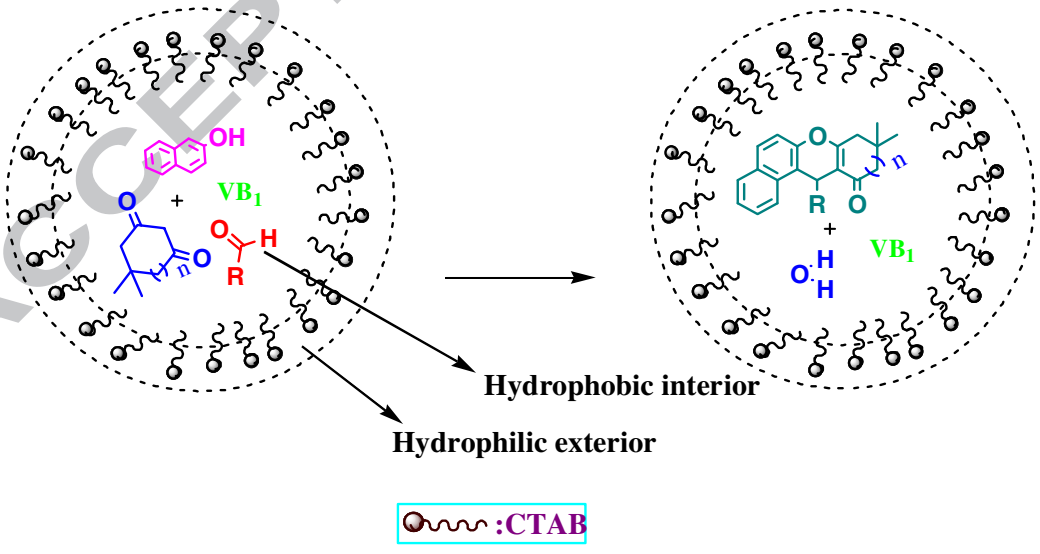
| Entry | Catalyst | Conditions | Time (min) | Yield (%) | Ref. |
|---|---|---|---|---|---|
| **1** | dodecatungsto phosphoric acid | 60°C/heat | 70 | 86 | 16 |
| **2** | $HClO_4$-$SiO_2$ | 80° C/heat | 72 | 89 | 14 |
| **3** | PTSA[a] | [bmim]$BF_4$/heat | 180 | 90 | - |
| **4** | $InCl_3$ | 120°C /heat | 30 | 84 | 17 |
| **5** | $I_2$ | 120°C /heat | | | 21 |
| **6** | TTAB[b] | $H_2O$/rt | 180 | 87 | - |
| **7** | $Sr(OTf)_2$ | 1,2-dichloroethane /80°C | 300 | 85 | 18 |
| **8** | TCT | 80 °C /neat | 50 | 90 | 20 |
| **9** | TBAF[c] | $H_2O$/reflux | 540 | 99 | 15 |
| **10** | $NaHSO_4/SiO_2$ | $CH_2Cl_2$/reflux | 300 | 91 | 19 |
| **11** | Silica sulfuric acid | 100°C | 30 | 95 | 22 |
| **12** | Thiamine hydrochloride | rt /aqueous micellar system | 25 | 93 | - |

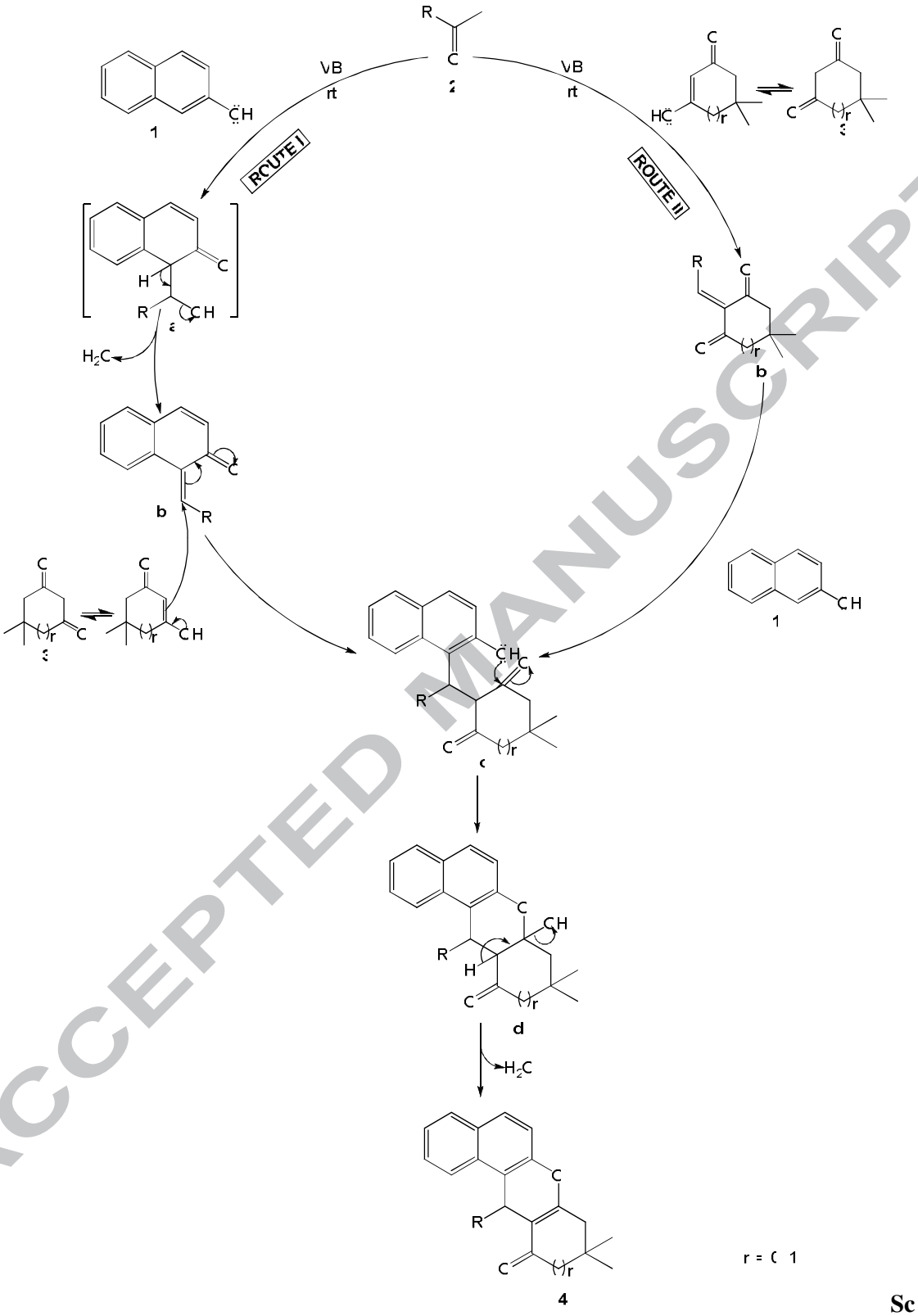
[a]para-Toluene sulphonic acid
[b]tetradecyltrimethylammonium bromide
[c]tetra(*n*-butyl)ammonium fluoride
Entry 12 : our work.

**Table 4:** Thiamine hydrochloride catalyzed condensation of aldehydes, 1,3-dicarbonyl compounds and *β*-naphthol

| Entry | R | n | product | Time (min) | Yield (%) | Mp (°C) | Colour of product |
|---|---|---|---|---|---|---|---|
| **1** | $C_6H_5$- | 1 | 4A | 25 | 92 | 147-149 | White solid |
| **2** | *p*-MeO.$C_6H_4$- | 1 | 4B | 32 | 86 | 208-210 | White solid |
| **3** | *o*-MeO.$C_6H_4$- | 1 | 4C | 30 | 87 | 164-166 | White solid |
| **4** | *p*-Me.$C_6H_4$- | 1 | 4D | 32 | 86 | 172-174 | White solid |
| **5** | *p*-Cl.$C_6H_4$- | 1 | 4E | 25 | 92 | 179-181 | White solid |
| **6** | *o*-Cl.$C_6H_4$- | 1 | 4F | 30 | 83 | 177-179 | White solid |
| **7** | *o,p*-$Cl_2$.$C_6H_3$- | 1 | 4G | 20 | 90 | 176-179 | White solid |
| **8** | *p*-HO.$C_6H_4$ | 1 | 4H | 33 | 78 | 223-125 | White solid |
| **9** | *m*-HO.$C_6H_4$ | 1 | 4I | 35 | 76 | 237-239 | White solid |
| **10** | *o*-$NO_2$.$C_6H_4$- | 1 | 4K | 30 | 84 | 221-223 | Pale yellow solid |
| **11** | *m*-$NO_2$.$C_6H_4$- | 1 | 4L | 32 | 84 | 166-168 | White solid |
| **12** | *p*-$NO_2$.$C_6H_4$- | 1 | 4M | 20 | 92 | 175-177 | White solid |
| **13** | 2-HO-3-MeO.$C_6H_3$- | 1 | 4N | 35 | 86 | 209-211 | White solid |
| **14** | 2-HO-3-EtO.$C_6H_3$- | 1 | 4O | 40 | 85 | 188-190 | White solid |
| **15** | 2-HO-5-$NO_2$.$C_6H_3$- | 1 | 4P | 30 | 88 | 262-264 | White solid |
| **16** | -CH=CH-$C_6H_5$ | 1 | 4Q | 40 | 87 | 146-148 | White solid |
| **17** | -$CH(CH_3)_2$ | 1 | 4R | 36 | 89 | 116-117 | White solid |
| **18** | -C.$(CH_3)_3$ | 1 | 4S | 37 | 90 | 110-111 | White solid |
| **19** | *p*-Cl.$C_6H_4$- | 0 | 4T | 38 | 90 | 233-234 | White solid |
| **20** | 3,4-$(CH_3)_2$.$C_6H_3$- | 0 | 4U | 35 | 91 | 223-224 | White solid |

From the mechanistic point of view it is proposed that the mechanism of formation of the target compounds may follow either **route I** or **route II** (Scheme 2). In **route I**, first step proceeds via the nucleophilic addition of *β*-naphthol to aldehyde, catalyzed by $VB_1$, to give an intermediate orthoquinone methide (o-QM) **Ib** via **Ia**. Subsequent Michael addition of the o-QM with dimedone followed by intramolecular cyclization and dehydration affords the desired product **4**. In second possible route (**route II**), first step proceeds via Knoevenagel condensation between diketone and aldehyde and second step is a Michael type conjugate addition followed by intramolecular cyclization and dehydration affords the desired product **4**. To confirm the reaction mechanism pathway, we performed the reaction via both the proposed routes of mechanism (**route I** and **route II**) by adding reagent sequentially. From **route I** we have isolated intermediate, orthoquinone methide (o-QM) **Ib**, which upon entrapment with active methylene compound via Michael addition followed by ring closure and dehydration gave the desired product. But when the reaction was performed according to **route II**, we have not got the intermediate. Since no intermediate could be observed or isolated via **route II**, the former mechanism (**route I**) fit for this reaction.






**Scheme 2:** Proposed mechanism for the benzoxanthen-11-ones

In summary we have developed an efficient one pot synthesis of 14-aryl-14H-dibenzo[a,j]xanthene and 12-aryl-8,9,10,12-tetrahydrobenzo[a]-xanthen-11-one derivatives by condensation of various substituted benzaldehydes, *β*-naphthol and dimedone using thiamine hydrochloride as a green catalyst under aqueous micellar system. This methodology is endowed with several advantages such as inexpensive as well as non-toxic catalyst, easy work-up procedure, use of non-hazardous solvent, low temperature. Only 5 mol% of thiamine hydrochloride gives the products in excellent yield within very short.

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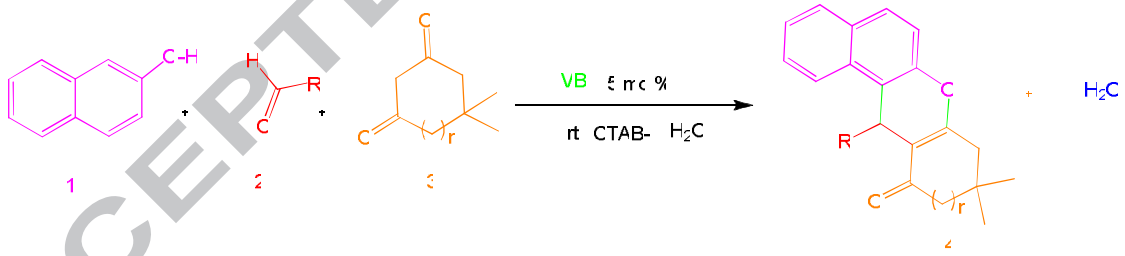
40. *General method for synthesis of compound 4:* To a mixture of *β*-naphthol 1 (1 mmol), aromatic/ non-aromatic aldehyde 2 (1mmol) and cyclic 1,3 dicarbonyl 3 (1mmol) in water/CTAB micellar system (10 mol% CTAB in 10 ml water), Thiamine hydrochloride (5 mol %) was added. This reaction mixture was allowed to stir vigorously at room temperature (45°C). Progress of the reaction was monitored by TLC (ethyl acetate: *n*-hexane; 2:8 v/v). After completion of the reaction, the solid obtained was collected by filtration and washed successively with warm water and cool aqueous ethanol. The crude product was recrystallized from ethanol to afford analytically pure desired product 4. *12-(4-Chlorophenyl)-9,9-dimethyl-8,9,10,12-tetrahydrobenzo[a]xanthen-11-one (4E)*: White solid; $R_f$ = 0.50 (1:9 EtOAc /Hexane), IR (KBr, $cm^{-1}$): 3078, 2915, 1637, 1367, 1219, 1164, 1081. $^1$H NMR (300 MHz, $CDCl_3$): δ 7.97 (d, *J* = 8.1 Hz, 1H), 7.83–7.79 (m, 2H), 7.48–7.14 (m, 7H), 5.70 (s, 1H), 2.60 (s, 2H), 2.37 (d, *J* = 16.2 Hz, 1H), 2.31 (d, *J* = 16.2 Hz, 1H), 1.14 (s, 3H), 0.94 (s, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$): δ 196.1, 164.7, 150.6, 148.7, 145.5, 132.9, 131.9, 129.9, 130.2, 128.9, 127.8, 125.9, 123.9, 122.6, 115.9, 115.1, 111.5, 50.1, 40.3, 33.8, 31.7, 28.9, 27.9. MS (FAB): m/z = 389.89 $[M+H]^+$. Anal. Calcd for $C_{25}H_{21}ClO_2$: C, 77.21%; H, 5.44. Found: C, 77.29; H, 5.36%.

## Graphical Abstract

**Thiamine hydrochloride as a promoter for the efficient and green synthesis of 12-aryl-8,9,10,12 tetrahydrobenzoxanthene-11-one derivatives in aqueous micellar medium**

Environmentally benign, three-component, one-pot integrated chemical process has been developed for synthesis of 12-aryl-8,9,10,12-tetrahydrobenzoxanthene-11-one by nucleophilic addition reaction between aldehyde and β-naphthol followed by Michael addition of dimedone, catalyzed by thiamine hydrochloride in aqueous micellar medium with excellent yield. Simple reaction conditions, no requirement of chromatographic separation, short reaction time, ease of isolation, use of inexpensive, easily recoverable and reusable catalyst makes this protocol very interesting from an economic and environmental perspective.

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