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Tetrabutyl ammonium hydrogen sulphate (TBAHS) Catalyzed Convenient and Greener Synthesis of Tetrahydrobenzo[a]xanthene-11-ones

Furqan Diwan,[a] Mohammad Mohsin,[a] Mohammad Shaikh,[b] Prasad Dixit,[c] Mazahar Farooqui*[a]

[a]*Department of Chemistry, Dr. Rafiq Zakaria, college for women, Aurangabad- 431001, India.*
[b]*Department of Chemistry, Dr. Rafiq Zakaria, college for women, Aurangabad-431001, India.*
[c]*Department of Chemistry, Dr. Rafiq Zakaria, college for women, Aurangabad-431001, India.*
**Corresponding author. Tel:+919422214785*
E-mail: mazahar_64@rediffmail.com; diwanfurqan@rediffmail.com*
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Abstract: A new efficient and green protocol was developed for the synthesis of Tetrahydrobenzo[*a*]xanthene-11-ones using Tetrabutyl ammonium hydrogen sulphate (TBAHS), as catalyst and water as a solvent under environmentally friendly conditions. The developed synthetic protocol represents a very simple and novel route for the synthesis of substituted Tetrahydrobenzo[*a*]xanthene-11-ones derivatives. the advantageous features of this methodology are environmentally friendly and operational simplicity, including excellent yields, shorter reaction time, mild reaction conditions and environmentally benign catalyst and solvent. Furthermore, analysis of the ADME parameters for synthesized compounds showed good drug like properties and can be developed as oral drug candidate.

Keywords: Tetrahydrobenzo[a]xanthene-11-ones; Tetrabutyl ammonium hydrogen sulphate (TBAHS); Water as a solvent; Green protocol; Operational simplicity.

Introduction

The present scenario of organic and green chemistry principles have encouraged the scientific community and researchers for the development of green and eco-friendly protocol for various organic transformation and motivated for the use of solid acid catalyst as an alternative to the conventional organic, mineral toxic and hazardous liquid acid catalyst like sulphuric acid, nitric acid, hydrochloric acid, methane sulphonic acid, trifluoroacetic acid likewise which cannot be use in stoichiometric amount. Whereas solid acid catalyst is economical industrially suitable and user-friendly owing their remarkable properties like negligible toxicity, easy availability, high stability and non-energy intensive methods for preparation and usage of the solid acid catalyst in the various organic transformation.

Focusing on the present scenario there is huge demand to introduce new eco-friendly and green methodologies that are efficient and more compatible with the environment. In this regard, our effort was to develop the greener and echo-friendly method by the scientific community the multicomponent reactions (MCRs) have been recognised as an extremely powerful tool in combinatorial chemistry and new drug discovery, since they offer good advantages over stepwise and conventional synthetic methods, to improve and promoting various new organic reactions and for the development of straight forward synthetic procedures to biologically active heterocycles [1].

Development of new synthetic routes to facilitate the synthesis of desired molecule is first choice of researchers. In this regard, lot of efforts have been made constantly to introduce new methodologies in the field of research and development that are efficient and more compatible with the environment. One of the most desirable approaches to address this challenge to establish a search of alternative to traditionally employed organic solvents, which suffer from various health issues and big concern for environment [2]. From the view point of green chemistry, water would be the perfect solvent to overcome this problem and carry out chemical reactions due to its safe, non-toxic, inexpensive, easy handling, availability and environmentally friendly nature [3]. However, the uses of water are rarely considered as a solvent for organic reactions. One of the reasons, why the chemists and researchers stay away from use of water the limited solubility of most organic compounds in pure water. Since solubility of substrate or reagent is necessary for reactivity, some alternative for improving the solubility of organic substrates that really helps in exploring the scope of water-based organic syntheses have been investigated [4]. The use of surface-active agents (surfactants) in aqueous media has been proved to enhance the reactivity of water-based reactions *via* formation of micelles or tubular cavities. The use of micellar and vesicle forming surfactants as catalysts in water is widespread and has been studied for different synthetic transformations/ multicomponent reactions in water [5].

Tetrabutylammonium hydrogen sulphate (TBAHS), is a stable, white solid (mp 169-171°C). It is widely used in various fields of chemistry as phase-transfer catalyst (PTC) and ion-pairing reagent as mobile phase additive in HPLC. It has been also used in a variety of organic transformations some of which include the syntheses of triarylpyridines [6], *N*-monosubstituted α-keto amides [7], cyclic and acyclic β-disubstituted, α,β-unsaturated ketones [8], 3-alkylated indoles [9], benzopyran-annulated pyrano[2,3-*c*]pyrazoles [10], *N*1-alkylated 3,4-dihydropyrimidine-2(1*H*)-ones [11], 2-*O*-deacetylated glucosyl hydroxamates [12], 1,2,3-triazoles [13], 1,8-dioxooctahydroxanthenes [14], β- and γ-amino ethers, morpholines and their higher homologues [15], etc

Xanthenes and benzoxanthenes constitute important classes of biodynamic heterocycles such as fluorone, fluorescein, rosamine, rhodamine, Rhodamine B and Rhodamine 6G are some well-known dyes that are derived from the xanthene nucleus and their synthesis has received much attention especially in the field of medicinal/pharmaceutical chemistry due to their wide range of biological/pharmacological activities, e.g., antibacterial [16], antimalarial [17], analgesic [18], anti-inflammatory [19] and antiviral [20]. Some xanthene-based compounds have found application as antagonists for inhibiting the action of zoxalamine and in photodynamic therapy [21]. In addition, their derivatives can be used as dyes [22], pH sensitive fluorescent materials for the visualization of biomolecular assemblies [23] and in laser technologies [24]. Among the xanthene-based

compounds, Tetrahydrobenzo[*a*]xanthene-11-ones are of interest and have great potential for further synthetic transformations [25]. Some novel methods for the synthesis of Tetrahydrobenzo[*a*]xanthene-11ones *via* multicomponent condensation reaction have been developed and catalysts such as ZrO_2-SO_3H [26], *N,N'*-dibromo-*N,N'*-1,2-ethanediyl-*bis*(*p*-toluenesulfonamide) [BNNTS] [27], (4-sulfobutyl)tris(4-sulfophenyl)phosphonium hydrogen sulphate [28], CAN [29], Manganese (IV) oxide [30], Lactic acid [31]; boric acid [32], Nano Nickel-Cobalt Ferrite [33], *N,N*-disulfo-1,1,3,3-tetramethylguanidinium carboxylate ionic liquid [34], Hap-encapsulated γ-Fe_2O_3 supported dual acidic heterogeneous catalyst [35], $Zr(HSO_4)_4$ [36], $NaHSO_4$.SiO_2 [37], strontium triflate [38], $LaCl_3$ [39], *p*-toluenesulfonic acid/ionic liquid([bmim]BF_4) [40], sulphated polyborate [41], dodecatungstophosphoric acid (PWA) [42], nanotitania-supported sulfonic acid [43], $InCl_3$/P_2O_5 [44], and $SiCl_4$ [45], Fe_3O_4@SiO_2-$SnCl_4$ [46] and visible light [47] as a promoter have been employed for their synthesis. However, in an era where green methods are desirable many of these methods are unsatisfactory as they involve the use of halogenated solvents, catalyst loadings of up to 30 mol %, low yields, drastic reaction conditions, prolonged reaction times and tedious isolation procedures. All of these disadvantages make further improvements for the synthesis of such molecules essential. Recently, synthetic methods that involve tetra (n-butyl) ammonium fluoride (TBAF) [48], proline triflate [49] and TTAB [50] in water have been described. However, the major problems associated with these routes are the need for higher/reflux conditions and longer reaction times. Therefore, it was thought worthwhile to develop a new greener and more convenient method for the preparation of Tetrahydrobenzo[*a*]xanthene-11-ones.

Considering the significance of surfactants and in continuation of our program to develop new and convenient synthetic protocols for the construction of bioactive heterocycles [51], herein we wish to report a highly efficient synthesis of 12-aryl-8,9,10,12-Tetrahydrobenzo[*a*]xanthen-11-ones using TBAHS in aqueous micellar form.

Experimental section

Chemistry

All the reagents and solvents used for the synthesis were purchased from Sigma Aldrich, Spectrochem and Molychem and were used as such without further purification. The melting points of all compounds were determined on a Toshniwal apparatus and are uncorrected. IR spectra were recorded on a Shimadzu FTIR-8400S spectrophotometer using KBr pellets. ^1H and ^{13}C NMR spectra were recorded in DMSO-d_6 using TMS as an internal standard on a Bruker spectrophotometer, respectively. Mass spectra of representative compounds were recorded on JEOL SX-102 spectrometer at 70 eV. Elemental microanalyses were carried out on a Carlo Erba1108 CHN analyzer. Thin layer chromatography was performed on pre-coated silica gel 60 F_{254} aluminium sheets (E. Merck, Germany) using various solvents systems and spots were identified by UV light and Iodine.

General experimental procedure for the synthesis of 12-aryl-8,9,10,12-tetrahydrobenzo[a]xanthen-11-ones 4(a-o): To a mixture of dimedone **1** (1 mmol), aldehyde **2** (1 mmol) and *β*-naphthol **3** (1 mmol) in water (5 mL) was added TBAHS (10 mol%). This reaction mass was allowed to stir vigorously at 60°C. Progress of the reaction was monitored by TLC (ethyl acetate:*n*-hexane, 2:8). After completion of the reaction, solid was accumulated at the bottom of the reaction flask which was collected by simple filtration and washed with warm water followed by ethanol.

This crude product **4** was then crystallized with ethanol to afford pure product without need of any further purification.

Spectral data of the products:

9,9-Dimethyl-12-phenyl-8,9,10,12-tetrahydro-11*H*-benzo[*a*]xanthen-11-one (**4a**): ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.97 (s, 3H), 1.13 (s, 3H), 2.25 (d, J=16 Hz, 1H), 2.32 (d, J=16.4 Hz, 1H), 2.58 (s, 2H), 5.71 (s, 1H), 7.06 (t, J=7.6, 1H), 7.18 (t, J=8, 2H), 7.32-7.46 (m, 5H), 7.77 (d, J=8.4 Hz, 1H), 7.79 (d, J=6.4 Hz, 1H), 8.00 (d, J=8.4Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 27.59, 29.72, 32.69, 35.14, 41.85, 51.34, 114.71, 117.46, 118.14, 124.11, 125.31, 126.65, 127.42, 128.65, 128.80, 128.85, 129.25, 131.85, 131.93, 145.18, 148.19, 164.30, 197.29 ppm. MS (FAB): m/z = [M]+ 354; FT-IR (KBr): υmax: 3053, 2957, 2891, 1649, 1620, 1596, 1469, 1452, 1372, 1241, 1226,1184, 1032, 837, 747, 723, 697.

12-(4-Chlorophenyl)-9,9-dimethyl-8,9,10,12-tetrahydrobenzo[*a*]xanthen-11-one (**4b**): ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.00 (s, 3H), 1.16 (s, 3H), 2.29 (d, 2H, J = 4 Hz), 2.59 (d, 2H, J = 4 Hz), 5.70 (s, 1H), 7.17-7.43 (m, 7H, Ar-H), 7.77-7.89 (m, 3H, Ar-H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 27.1, 29.3, 32.5, 34.3, 41.9, 50.9, 113.1, 116.8, 117.3, 123.9, 125.0, 127.2, 128.7, 129.4, 130.2, 131.5, 131.9, 132.6, 143.3, 145.1, 150.8, 164.2, 196.9; IR (KBr, cm^{-1}): ν 2952, 1648, 1597, 1373, 1231, 1184, 823; ES-MS: 389.14 [M+2], 391.13.

12-(4-Methylphenyl)-8,9,10,12-tetrahydrobenzo[*a*]xanthen-11-one (**4c**): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.99-2.06 (m, 2H), 2.22 (s, 3H), 2.38-2.46 (m, 2H), 2.67-2.74 (m, 2H), 5.72 (s, 1H), 6.99 (d, J=8 Hz, 2H), 7.23 (d, J=8 Hz, 2H), 7.34 (d, J=8.8 Hz, 1H), 7.35-7.50 (m, 2H), 7.76 (d, J=7.2 Hz, 1H), 7.78 (d, J=8.8 Hz, 1H), 7.98 (d, J=8.4 Hz, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.74, 21.47, 28.17, 34.70, 37.53, 116.17, 117.44, 118.35, 123.17, 124.17, 125.32, 127.43, 128.83, 129.20, 129.47, 131.89, 131.96, 136.19, 142.69, 148.21, 165.94, 197.50 ppm. FT-IR (KBr): υ_{max}: 2947, 1647, 1622, 1596, 1509, 1406, 1372, 1253, 1224,1188, 1032, 838, 808, 742. MS (FAB): m/z = [M]+ 340.

9,9-Dimethyl-12-(4-methoxyphenyl)-8,9,10,12-tetrahydrobenzo[*a*]xanthen-11-one (**4d**): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.98 (s, 3H), 1.12 (s, 3H), 2.25 (d, J=16 Hz, 1H), 2.32 (d, J=16.4 Hz, 1H), 2.57 (s, 2H), 3.69 (s,3H), 5.66 (s,1H), 6.71 (d, J=8.4 Hz, 2H), 7.20-7.27 (m, 2H), 7.32 (d, J=8.8 Hz, 1H), 7.38 (t, J=8 Hz, 1H), 7.44 (t, J=8 Hz, 1H), 7.76 (d, J=9.2 Hz, 1H), 7.78 (d, J=9.2 Hz, 1H), 7.99 (d, J=8.4 Hz, 1H) ppm. FT-IR (KBr): υ_{max}: 2957, 2898, 1644, 1611, 1594, 1509, 1460, 1371, 1245, 1249, 1223, 1164, 1027, 1025, 833, 812, 747. MS (FAB): m/z = [M]+ 384.

12-(2-Nitrophenyl)-9,9-dimethyl-8,9,10,12-tetrahydrobenzo[*a*]xanthen-11-one (**4g**): ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.87 (s, 3H), 1.10 (s, 3H), 2.19 (d, 2H, J = 4Hz), 2.52 (d, 2H, J = 4 Hz), 6.56 (s, 1H), 7.02 (d, 1H, J = 8 Hz), 7.18-7.46 (m, 5H, Ar-H), 7.75-7.88 (m, 3H, Ar-H), 8.51 (d, 1 H, J = 8 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 27.2, 29.5, 32.1, 34.6, 41.1, 51.4, 112.9, 116.6, 117.8, 124.1, 124.7, 126.9, 127.4, 128.1, 128.7, 129.5, 129.9, 131.3, 131.7, 132.2, 134.0, 141.5, 149.2, 163.9, 196.1; IR (KBr, cm^{-1}): ν 2957, 1651, 1595, 1537, 1376, 1348, 1226, 1174, 818; ES-MS: 400.16 [M+].

9,9-Dimethyl-12-(4-bromophenyl)-8,9,10,12-tetrahydrobenzo[*a*]xanthen-11-one (**4k**): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.97 (s, 3H), 1.13 (s, 3H), 2.25 (d, J=16.4 Hz, 1H), 2.32 (d, J=16 Hz, 1H), 2.58 (s, 2H), 5.67 (s,1H), 7.22 (d, J=7.2 Hz, 2H), 7.29 (d, J=7.2 Hz, 2H), 7.33 (d, J=9.2 Hz, 1H), 7.40 (t, J=7.6 Hz, 1H), 7.45 (t, J=7.6 Hz, 1H), 7.78 (d, J=7.2 Hz, 1H), 7.80 (d, J=6.8 Hz, 1H), 7.91 (d, J=8 Hz, 1H) ppm. ^{13}C NMR

(125 MHz, $CDCl_3$): δ = 27.59, 29.72, 32.68, 34.70, 41.83, 51.29, 114.18, 117.41, 117.46, 120.54, 123.88, 125.46, 127.56, 128.92, 129.54, 130.62, 131.64, 131.77, 131.95, 144.19, 148.17, 164.49, 197.27 ppm. FT-IR (KBr): υmax: 2966, 2876, 1640, 1622, 1593, 1484, 1372, 1274, 1220, 1174, 1071, 1010, 837, 811, 756, MS (FAB): m/z = [M]+ 432, $[M + 2]^+$ 434.

12-[4-(Benzo[*d*][1,3]dioxol-5-yl)]-9,9-dimethyl-8,9,10,12tetrahydrobenzo[*a*] xanthen-11-one (**4l**): ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.01 (s, 3H), 1.13 (s, 3H), 2.28 (s, 2H), 2.56 (s, 2H), 5.62 (s, 1H), 5.80 (d, 1H, J = 1.2 Hz) 5.84 (d, 1H, J = 1.2 Hz), 6.59 (d, 1H, J = 8 Hz), 6.77 (td, 2H, J = 8, 2 Hz), 7.26-7.48 (m, 3H), 7.72-7.79 (m, 2H), 7.95 (d, 1H, J = 8 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 26.9, 29.6, 32.6, 34.7, 41.4, 51.7, 101.5, 111.2, 113.8, 115.1, 117.6, 122.3, 123.8, 124.8, 128.3, 128.8, 129.4, 130.1, 131.6, 132.5, 140.0, 145.5, 146.7, 149.1, 163.4, 197.6; IR (KBr, cm^{-1}): v 2948, 1639, 1592, 1368, 1234, 1178, 1039, 829; ES-MS: 399.21 [M+].

12-(Thiophen-2-yl)-9,9-dimethyl-8,9,10,12-tetrahydrobenzo[*a*]xanthen-11-one (**4m**): ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.05 (s, 3H), 1.14 (s, 3H), 2.34 (s, 2H), 2.56 (s, 2H), 6.02 (s, 1H), 6.72–6.75 (m, 2 H), 6.99 (dd, 1H, J = 4Hz), 7.40-7.51 (m, 2H), 7.75-7.82 (m, 2H), 8.01 (d, 1H, J = 8 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 27.5, 29.4, 32.9, 34.8, 41.8, 51.2, 113.4, 115.2, 117.7, 123.0, 126.5, 127.2, 127.9, 129.6, 130.3, 130.8, 132.1, 132.6, 135.4, 139.7, 144.6, 162.7, 197.6; IR (KBr, cm^{-1}): v 2947, 1638, 1593, 1372, 1225, 1061, 724; ES-MS: 361.13 [M+].

12-(Furan-2-yl)-9,9-dimethyl-8,9,10,12-tetrahydrobenzo[*a*]xanthen-11-one (**4n**): ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.06 (s, 3H), 1.16 (s, 3H), 2.38 (s, 2H), 2.62 (s, 2H), 6.02 (s, 1H), 6.76–6.81 (m, 2 H), 7.01 (dd, 1H, J = 4Hz), 7.46-7.58 (m, 2H), 7.80-7.85 (m, 2H), 8.03 (d, 1H, J = 8 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 27.6, 29.6, 33.0, 34.9, 41.6, 51.3, 112.2, 114.7, 123.5, 123.9, 126.6, 127.1, 128.2, 128.8, 129.5, 129.9, 130.3, 132.2, 133.4, 136.1, 152.7, 162.9, 198.2; IR (KBr, cm^{-1}): v 2951, 1641, 1596, 1362, 1231, 1058, 735; ES-MS: 345.09 [M+].

12-(Indol-3-yl)-9,9-dimethyl-8,9,10,12-tetrahydrobenzo[*a*]xanthen-11-one (**4o**): ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.91 (s, 3H), 1.12 (s, 3H), 2.24 (d, 2H, J = 6 Hz), 2.61 (s, 2H), 6.00 (s, 1H), 6.98 (td, 2H, J = 8, 2 Hz), 7.16 (d, 2H, J = 4 Hz), 7.31-7.37 (m, 3H), 7.48 (d, 1H, J = 8 Hz), 7.71 (d, 2H, J = 8 Hz), 8.09 (d, 1H, J = 8 Hz), 8.16 (s, 1H, -NH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 26.5, 28.9, 31.8, 34.2, 41.2, 51.0, 111.8, 114.1, 116.9, 117.7, 119.7, 120.2, 123.9, 124.2, 125.1, 126.1, 128.5, 129.2, 129.6, 130.7, 131.9, 135.4, 141.2, 148.8, 164.2, 197.1; IR (KBr, cm-1): v 3363, 1648, 1597, 1365, 1229, 1175, 1142, 796; ES-MS: 394.19 [M+].

Computational Study

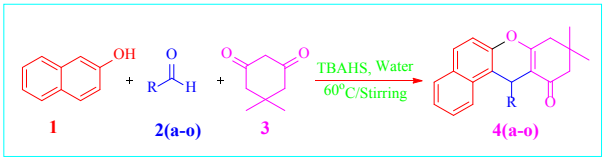
ADME Properties

The success of a drug is determined not only by good efficacy but also by an acceptable ADME (absorption, distribution, metabolism and excretion) profile. In the present study, we have calculated molecular volume (MV), molecular weight (MW), logarithm of partition coefficient (miLog *P*), number of hydrogen bond acceptors (n-ON), number of hydrogen bonds donors (n-OHNH), topological polar surface area (TPSA), number of rotatable bonds (n-ROTB) and Lipinski's rule of five [52] using Molinspiration online property calculation toolkit [53]. Absorption (% ABS) was calculated by: % ABS = 109-(0.345×TPSA) [54] Drug-likeness model score (a collective property of physic-chemical properties, pharmacokinetics and pharmacodynamics of a compound is represented by a numerical value) was computed by MolSoft [55] software.

Result and discussion

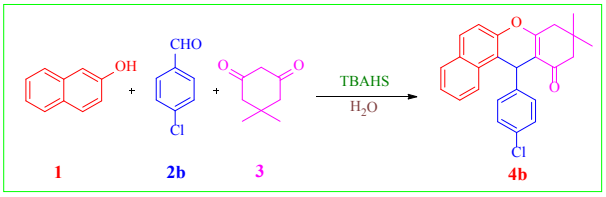
Chemistry

An efficient and greener protocol for the synthesis of 12-aryl-8,9,10,12-Tetrahydro-benzo[*a*]xanthen-11-one using Tetrabutyl ammonium hydrogen sulphate (TBAHS), at 60°C in water is described. The pronounced catalytic effect of TBAHS is introduced for the first time in organic synthesis of tetrahydro-benzo[*a*]xanthen-11-ones (**Scheme 1**).



Scheme 1. Synthesis of tetrahydro-benzo[*a*] xanthen-11-ones in water.

For our initial study, reaction of *β*-naphthol **1**, 4-chloro benzaldehyde **2b**, and dimedone **3** in water using different catalyst was considered as a standard model reaction (**Scheme 2**).



Scheme 2. Standard model reaction

In search of the best experimental reaction conditions, the model reaction was performed under catalyst-free conditions at 60°C. Unfortunately, even after prolong reaction,the reaction proceeds to 20% (**Table 1**, entry 1). Therefore, it was thought that for initiation of the reaction, intervention of catalyst is necessary. During this investigation, Tetrabutyl ammonium bromide (TBAB), Cetyltrimethyl ammonium bromide (CTAB), Methyltriphenyl phosphonium bromide (MTPPB), Cetylpyridinium chloride (CPC), Sodium dodecyl sulphate (SDS), Tetraethyl ammonium bromide (TEAB) and TBAHS phase transfer catalyst used at 60°C. From the preliminary studies, it was found that product obtained in low yields, i.e., 40%, 35%, 45%, 50%, 60, 40% and 90% respectively (**Table 1**, entry 2-8). Similarly, p-Toluene sulphonic acid (PTSA) and Methane sulphonic acid (MSA) also used as acidic catalyst to catalyze this reaction but the product observed in low yield 60% and 65% respectively (**Table 1**, entry 9-10).

Table 1. Optimization of catalyst[a].

Entry	Catalyst	Temp (°C)	Time (hr)	Yield (%)
1	-	60	4	20
2	TBAB	60	4	40
3	CTAB	60	4	35
4	MTPPB	60	4	45
5	CPC	60	4	50
6	SDS	60	4	60
7	TEAB	60	4	40
8	TBAHS	60	2	90
9	PTSA	60	4	60
10	MSA	60	4	65

[a] *Reaction conditions*: **1** (1 mmol), **2b** (1 mmol), **3** (1 mmol) and catalyst in water (5 mL); [b]Isolated yields

From this, it was concluded that the TBAHS is far superior to other catalysts for efficient catalysis. During this investigation, efforts were mainly focused on the effect of temperature on the reaction. For evaluation of temperature effect, this reaction was performed at room temperature, 40, 60 ºC, 80 ºC and 90 ºC conditions (**Table 2**, entries 1-5) and found out that at 60ºC the product obtained was 90% (**Table 2**, Entry 3). At room temperature and 40ºC reaction does not goes to completion resulted into lower product yield 20 and 65% respectively (**Table 2**, Entry 1 and 2). While at higher temperature condition 80 and 100 ºC the

product was obtained in excellent 90% yield (**Table 2**, entry 4 and 5) so decided to kept the reaction temperature 60ºC as an optimization temperature condition.

To optimize the catalyst concentration, the model reaction was performed under catalyst-free conditions at 60°C. Unfortunately, even after long reaction time the reaction proceeds to 20% (**Table 3**, entry 1). Therefore, it was thought that for initiation of the reaction, intervention of catalyst is necessary. In the next step, we have screened 2.5 mol% of TBAHS at 60 °C as catalysts for the model reaction. Surprisingly, the product **4a** was obtained in 50% yield for 4 hr (**Table 3**, entry 2).

Encouraged by this result, we have changed the amount of TBAHS from 2.5 mol% to 20 mol% and the results are summarized in **Table 3**. Hence, the 10 mol% of TBAHS is sufficient to carry out the reaction smoothly (**Table 3**, entry 4). Excess amount of catalyst did not increase the yield of product neither reduces the time (**Table 3**, entry 5 and 6).

Table 2. Optimization of Temperature[a].

Sr. No.	Catalyst	Temp (ºC)	Time (hr)	Yield[b] (%)
1	TBAHS	RT	4	20
2	TBAHS	40	4	65
3	TBAHS	60	2	90
4	TBAHS	80	2	90
5	TBAHS	90	2	90

[a]*Reaction conditions*: **1** (1 mmol), **2b** (1 mmol), **3** (1 mmol), TBAHS, in water (5 mL); [b]Isolated yields.

It is noteworthy to point out that, addition of TBAHS converted the initially floating reaction mass into a homogeneous mixture, which on stirring turned out into a white turbid emulsion. This observation implied that there was formation of micelles or micelle-like colloidal aggregates.

Table 3. Screening of Catalyst.[a]

Sr. No.	Mol%	Temp (ºC)	Time (hr)	Yield[b] (%)
1	-	60	4	20
2	2.5	60	4	50
3	5	60	5	65
4	10	60	2	90
5	15	60	2	90
6	20	60	2	90

[a]*Reaction conditions*: **1** (1 mmol), **2b** (1 mmol), **3** (1 mmol), TBAHS (mol%), in water (5 mL); [b]Isolated yields

It is well understood that dehydration reactions are quite difficult to carry out in solvent like water; hence the water generated during the reaction has to be remove. To shift the equilibrium towards the side of the dehydrated product. In spite of that, by introducing surfactant (TBAHS) dehydration has been taken place successfully in water. The catalytic effect of TBAHS and characteristic of micellar solution may be attributed to the hydrophobic nature of organic substrates. The emulsion droplets are observed in water in the presence of surfactant and substrate molecules.

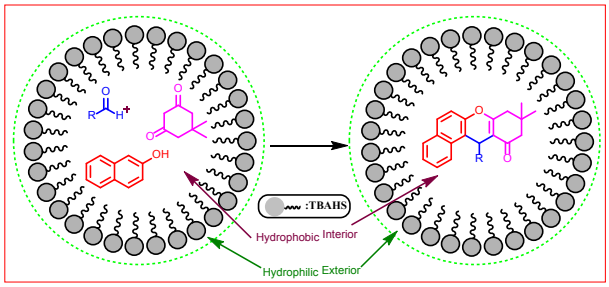


Figure 1. Schematic diagram representing the role of TBAHS

It is suggested that most of the organic substrates are aggregated in these spherical droplets, which behave as a hydrophobic reaction site and consequently enhance the effective concentration of the organic molecules, which might be accelerating the rate of reaction *via* effect of concentration. In micellar solution,

organic molecules are rippled from water molecules towards the hydrophobic core of micelle droplets thus inducing effect of collisions between organic molecules which eventually enhance the reaction rate and result in rapid reactions in water. Hydrophobic interior of the micelles quickly excludes the water molecules generated during the reaction, thus diversify the equilibrium towards the desired product. Hence increase the product yield [56]. It is well demonstrated schematically by **Figure 1**.

A plausible mechanistic path leading to the formation of Tetrahydrobenzo[*a*]xanthen-11-one can be outlined as follows- formation of tetrahydrobenzo[*a*]xanthen-11-one can be outlined as follows- the aldehydic carbonyl oxygen gets activated by the TBAHS through intermolecular hydrogen bonding followed by nucleophilic addition of 2-naphthol leads to the *ortho*-quinone methide (*o*-QM) intermediate. Furthermore, dimedone addition through Michael addition generated *o*-QM followed by the attack of phenolic-OH group of *o*-QM to the carbonyl carbon of dimedone provides a cyclic hemiketal that on dehydration affords the final product (**Figure 2**).

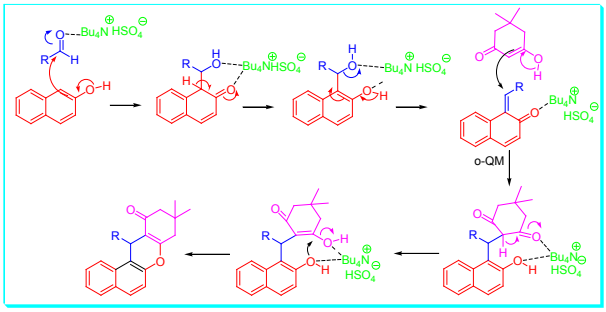
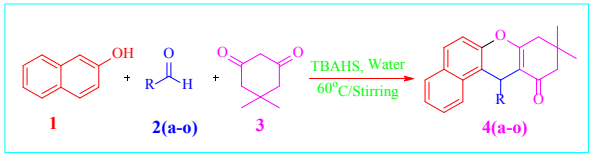


Figure 2. Plausible mechanistic path to the formation of Tetrahydrobenzo[*a*]xanthen-11-one

To generalize the synthetic procedure, various electronically divergent aryl aldehydes were treated with *β*-naphthol and dimedone under optimized reaction conditions and all these substrates were found to be equally amenable to these conditions. Interestingly, some heteroaryl aldehydes also underwent the reaction smoothly. Representative results are summarized in **Table 4**. Formation of the products was confirmed on the basis of ^{1}H NMR, ^{13}C NMR and mass spectroscopic analysis (*Supporting Information*).

Table 4. Synthesis of 12-aryl-8,9,10,12-tetrahydrobenzo[a]xanthen-11-ones **4(a-o)**



Entry	Comp.	R	Time (h)	Yield[a] (%)	M.P.[b] (°C)
1	**4a**	Ph	2	90	150-151
2	**4b**	4-Cl-Ph	2	90	182-184
3	**4c**	4-Me-Ph	2.5	85	174-176
4	**4d**	4-OMe-Ph	3	89	205-206
5	**4e**	4-F-Ph	2.5	85	184-186
6	**4f**	2-Cl-Ph	2	86	177-178
7	**4g**	2-NO_2-Ph	2	89	222-224
8	**4h**	3-NO_2-Ph	2.5	89	169-170
9	**4i**	4-NO_2-Ph	2.5	86	180-181
10	**4j**	4-OH-Ph	3	88	221-223
11	**4k**	4-Br-Ph	2	87	187-189
12	**4l**	Piperonyl	3	85	211-212
13	**4m**	2-Thienyl	4	82	176-178
14	**4n**	2-Furyl	4	84	170-172
15	**4o**	3-Indolyl	5	85	202-204

[a]Isolated yields; [b]Melting points matches with literature values.

Computational Study

ADME Properties

A computational study of all the synthesized 12-aryl-8,9,10,12-tetrahydrobenzo[a]xanthen-

11-ones 4(a-o) was performed for prediction of ADME properties and the value obtained is presented in **Table 5**. It is observed that, the compounds exhibited a good % ABS (% absorption) ranging from 84.11 to 99.92%. Furthermore, all the compounds show miLog P > 5). A molecule likely to be developed as an orally active drug candidate should show no more than one violation of the following four criteria: miLog P (octanol-water partition coefficient) ≤ 5, molecular weight ≤ 500, number of hydrogen bond acceptors ≤ 10 and number of hydrogen bond donors ≤ 5 [57]. The larger the value of the drug likeness model score, the higher is also probability that the particular molecule will be active. All the tested compounds followed the criteria for orally active drug and therefore, these compounds may have a good potential for eventual development as oral agents.

Conclusion

In conclusion, we have developed an exceedingly simple, mild, clean and greener synthetic protocol for Tetrahydrobenzo[*a*]xanthene-11-one. In this method, application of TBAHS has been first time introduced for organic transformation of 12-aryl-8,9,10,12-tetrahydro-benzo[*a*]xanthen-11-one. Water is not only inexpensive and environmentally benign solvent but also plays a distinguished role in reactivity and selectivity. TBAHS catalyst catalysed the reaction efficiently in short reaction times, without using any harmful organic catalyst and solvents. Furthermore, analysis of the ADME parameters for synthesized compounds showed good drug like properties and can be developed as oral drug candidate.

Conflict of interest

There is no conflict of interests regarding the publication of this article.

Table 5. Pharmacokinetic parameters important for good oral bioavailability

Cpd	% ABS	TPSA (A^2)	n-ROTB	MV	MW	miLog *P*	n-ON	n-OHNH	Lipinski violation	Drug-likeness model score
Rule	-	-	-	-	< 500	≤ 5	< 10	< 5	≤ 1	-
4a	99.92	26.30	1	333.20	354.45	6.02	2	0	1	-0.23
4b	99.92	26.30	1	346.74	388.89	6.70	2	0	1	0.29
4c	99.92	26.30	1	349.76	368.48	6.47	2	0	1	-0.13
4d	96.73	35.54	2	358.75	384.48	6.07	3	0	1	0.12
4e	99.92	26.30	1	338.13	372.44	6.18	2	0	1	0.20
4f	99.92	26.30	1	346.74	388.89	6.65	2	0	1	0.00
4g	84.11	72.13	2	356.54	399.45	5.93	5	0	1	-0.42
4h	84.11	72.13	2	356.54	399.45	5.95	5	0	1	-0.25
4i	84.11	72.13	2	356.54	399.45	5.98	5	0	1	-0.29
4j	92.94	46.53	1	341.22	370.45	5.54	3	0	1	0.25
4k	99.92	26.30	1	351.09	433.35	6.83	2	0	1	-0.01
4l	93.55	44.77	1	357.13	398.46	5.91	4	0	1	-0.08
4m	99.92	26.30	1	323.91	360.48	5.92	2	0	1	-0.26
4n	95.38	39.45	1	314.77	344.41	5.28	3	0	1	-0.30
4o	94.47	42.10	1	362.18	393.49	6.17	3	1	1	-1.08

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