CERIUM(III) CHLORIDE

In past decades Kagan and Luche revealed that Lanthanide reagents had experienced an extensive growth in organic chemistry.\textsuperscript{1,2} The applications of Lanthanides have been covered almost every aspect of organic transformations and they represent ideal promoters for various organic synthesis. Lanthanides are often called as rare earth elements, for example, cerium is more abundant element than cobalt, tin and zinc in Lanthanide series.

Generally, metal triflate promoters are rather expensive and their uses for the large scale synthetic operation could not be economical. Thus, the expensive issues associated with the use of Lanthanides reagents shifted the attention towards CeCl\textsubscript{3}.7H\textsubscript{2}O. Cerium shows +4 and +3 oxidation state. Cerium(IV) compounds were extensively used as convenient and effective one-electron oxidants for a variety of transformations.\textsuperscript{3} However, the most stable oxidation state of cerium is +3 and cerium(III) chloride heptahydrate (CeCl\textsubscript{3}.7H\textsubscript{2}O)\textsuperscript{4} is the most common source of Ce\textsuperscript{3+}. CeCl\textsubscript{3}.7H\textsubscript{2}O is a commercially Lanthanide reagent which is water tolerant, easy to handle and inexpensive.

The both hydrated and anhydrous form of cerium(III) chloride have been used in organic synthesis. Due to this reason, the crucial oxophilic character of cerium(III) chloride is governing chemo-regio-, and stereoselectivity promoted transformations.\textsuperscript{5} Cerium(III) chloride heptahydrate (CeCl\textsubscript{3}.7H\textsubscript{2}O) have received much attention due to its low toxicity energy saving, high purity delivering products, stability, green and efficient Lewis acid in modern organic synthesis.\textsuperscript{6}

Application in Organic Synthesis

As already mentioned, being electrophilic in nature, CeCl\textsubscript{3}.7H\textsubscript{2}O acts as Lewis acid and hence facilitates various organic transformations.
In early 1985’s Imamoto and co-workers widely applied anhydrous cerium(III) chloride as the reagent to promote the nucleophilic addition of Grignard reagents (1) to ketones (2) for the synthesis of tertiary alcohols (3) (Scheme 1).  

\[
\begin{align*}
\text{RMgX} & \rightarrow \text{CeCl}_3 \\
\text{THF or THF/ether, 0 \degree C} & \rightarrow \text{OH} \\
& \rightarrow R^1 - C - R^2 \\
& \rightarrow R
\end{align*}
\]

R = C\text{H}_5, n-\text{Bu}, i-\text{Pr}, \text{Ph}, \text{H}_2\text{C} = \text{CH}; R^1 = \text{PhHC} = \text{CH}, R^2 = \text{CH}_3 \\
R^1 = \text{PhHC} = \text{CH}, R^2 = \text{Ph}; R^1 = R^2 = \text{PhCH}_2, i-\text{Pr}; X = \text{Br, Cl}

Scheme 1

Non-aqueous selective conversion of dioxolanes (4) to carbonyl compounds (2) was catalyzed by cerium(III) chloride heptahydrate in acetonitrile (Scheme 2).  

\[
\begin{align*}
\text{CeCl}_3.\text{7H}_2\text{O, CH}_3\text{CN} & \rightarrow \text{R}^1 - \text{O} - \text{R}^2 \\
& \rightarrow \text{R}^1 - \text{R}^2
\end{align*}
\]

R\text{I} = R\text{II} = c-\text{Cyclohexyl}; R\text{I} = R\text{II} = c-\text{Cyclopentenyl} \\
R\text{I} = \text{CH}_3, \text{C}_6\text{H}_5, \text{C}_6\text{H}_5\text{CH}_2\text{CH}_2 \\
R\text{II} = \text{CH}_2\text{COOEt, CH}_2\text{CH}_2\text{OH, C}_6\text{H}_5, 5-\text{NO}_2-1-\text{Hexanone}

Scheme 2

Michael addition of 1,3-dicarbonyl compounds (5) with methylylacrylate (6) was catalyzed by cerium chloride heptahydrate to afford Michael adduct (7), through a simple solvent-free reaction under microwave irradiations (Scheme 3).  

\[
\begin{align*}
\text{CeCl}_3.\text{7H}_2\text{O} & \rightarrow \text{Me} + \text{Me} \\
& \rightarrow \text{Me} \\
& \rightarrow \text{Me}
\end{align*}
\]

R\text{I} = R\text{II} = \text{Me, Et}

Scheme 3
The regioselective synthesis of cyclic $\alpha,\beta$-chloro enones (9) from $\alpha,\beta$-epoxy ketones (8) was carried out using cerium(III) chloride under hydrous or anhydrous conditions (Scheme 4). 

\[ \begin{align*}
\text{CeCl}_3\cdot 7\text{H}_2\text{O} & \quad \text{MeOH/H}_2\text{O} \\
(8) & \quad (9)
\end{align*} \]

Scheme 4

\[ \text{n = 0, 1, 2; R}^1 = \text{R}^2 = \text{R}^3 = \text{H} \\
\text{n = 0, 1; R}^1 = \text{Me}; \text{R}^2 = \text{R}^3 = \text{H} \\
\text{n = 1; R}^1 = \text{R}^3 = \text{Me}; \text{R}^2 = \text{H} \\
\text{n = 1; R}^1 = \text{R}^3 = \text{H}; \text{R}^2 = \text{Me}
\]

The dehydration of $\beta$-hydroxy ketones or $\beta$-hydroxy esters (10) was reported for the conversion of these compounds (10) to the corresponding $\alpha,\beta$-unsaturated derivatives (11). Cerium(III) chloride heptahydrate in combination with sodium iodide in refluxing acetonitrile was found to act as an efficient reagent for this conversion (Scheme 5). 

\[ \begin{align*}
\text{CeCl}_3\cdot 7\text{H}_2\text{O}, \text{NaI} & \quad \text{CH}_3\text{CN, reflux} \\
(10) & \quad (11)
\end{align*} \]

\[ \begin{align*}
\text{R} & = \text{H, Me, Ph, C}_4\text{H}_3\text{O} \\
\text{X} & = \text{Ph, Me, Et, Ph, OEt, Bu, (CH}_3)_2\text{CCH}_2\text{O, 'Bu}
\end{align*} \]

Scheme 5

Cerium(III) chloride was found to be an effective catalyst for the chemoselective reduction of ketones (2) to alcohols (12) in the presence of pyrrolidine in methanol (Scheme 6).
A convenient and efficient synthesis of 1,2-azidoalcohols (14) was achieved by ring opening of epoxides (13) using cerium(III) chloride heptahydrate with sodium azide in acetonitrile (Scheme 7).\textsuperscript{13}

\[
\text{R} - \text{O} \quad \overset{\text{CeCl}_3.\text{7H}_2\text{O}/\text{NaN}_3}{\text{CH}_3\text{CN}, \text{H}_2\text{O 9:1, 3 h, reflux}} \quad \text{OH} \quad \text{N}_3
\]

\(\text{R} = \text{C}_6\text{H}_5, 3,5-(\text{CH}_3)_2\text{C}_6\text{H}_3, 3,5\text{-Cl}_2\text{C}_6\text{H}_3, 2\text{-Naphthyl}\)

Scheme 7

The Michael addition of substituted indoles (15) to \(\alpha,\beta\)-unsaturated ketones (16) was catalyzed by CeCl\(_3\).7H\(_2\)O-NaI combination supported on silica gel to give the corresponding 3-(3-oxoalkyl)indole derivatives (17) (Scheme 8).\textsuperscript{14}

CeCl\(_3\).7H\(_2\)O-NaI system promoted the allylation reaction of aldehydes (18) with allyltributylstannane (19) for the preparation of homoallylic alcohols (20) in acetonitrile (Scheme 9).\textsuperscript{15}
\[ \text{R} = \text{C}_6\text{H}_5, 4-\text{H}_3\text{C}_6\text{H}_4, 4-\text{F}_3\text{C}_6\text{H}_4, 4-\text{CNC}_6\text{H}_4, 4-\text{O}_2\text{N}_3\text{C}_6\text{H}_4, 3-\text{O}_2\text{N}_3\text{C}_6\text{H}_4, \\
4-\text{MeOC}_6\text{H}_4, 2-\text{MeOC}_6\text{H}_4, c\text{-Cyclohexyl, C}_6\text{H}_5\text{CH}_2\text{CH}_2, \text{ClCH}_2(\text{CH}_2)_4, \\
\text{CH}_3\text{HC}=\text{CHCH}_2 \]

Scheme 9

\[ \text{R,}R'-\text{Disubstituted ureas (23) were efficiently synthesized by reactions of urea (21) with a variety of amines (22) in water under microwave irradiation using CeCl}_3.7\text{H}_2\text{O}-\text{KI as catalyst (Scheme 10).}^{16} \]

\[ \begin{align*}
\text{H}_2\text{N} & \quad \text{O} \\
\text{R} & \quad \text{H}_2\text{N} + \text{R} - \text{NH}_2 \\
\text{CeCl}_3.7\text{H}_2\text{O-KI} & \quad \text{H}_2\text{O}, \text{MW} \\
\text{R} & \quad \text{C}_6\text{H}_5, 4-\text{MeC}_6\text{H}_4, 2-\text{MeOC}_6\text{H}_4, 4-\text{MeOC}_6\text{H}_4, 2-\text{ClC}_6\text{H}_4, 4-\text{ClC}_6\text{H}_4, \\
4-\text{BrC}_6\text{H}_4, 4-\text{O}_2\text{N}_3\text{C}_6\text{H}_4, 1-\text{Naphthyl, C}_2\text{H}_5, n-C_4\text{H}_9, C_6\text{H}_5\text{CH}_2, \\
4-\text{Pyridine, 2-Thiazole} 
\end{align*} \]

Scheme 10

Tetrahydropyranylation of hydroxyl compounds (24) with 3,4-dihydro-2\(H\)-pyran (DHP) (25) was achieved by using CeCl\(_3\).7H\(_2\)O-NaI system to give the tetrahydropyranyl (THP) ethers (26) under solvent-free conditions (Scheme 11).\(^{17}\)

\[ \begin{align*}
\text{R} & \quad \text{OH} + \\
\text{CeCl}_3.7\text{H}_2\text{O (2-5 mol%)} & \quad \text{NaI (2-5 mol%)} \\
\text{rt} & \quad \\
\text{R} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{R} & \quad \text{OH} \end{align*} \]

Scheme 11
A convenient method for the preparation of β-acetamido carbonyl compounds (28) was described by multi-component reactions of aromatic aldehydes (18), acetophenone (27) and acetonitrile in the presence of acetyl chloride and 10 mol% CeCl₃.7H₂O at room temperature (Scheme 12).¹⁸

![Scheme 12](image_url)

R = C₆H₅, 4-MeC₆H₄, 4-Br, 4-ClC₆H₄, 4-O₂NC₆H₄, 3-O₂NC₆H₄, 4-MeOC₆H₄, 3,4-(MeO)₂C₆H₃, 2-O₂NC₆H₄, 3,4,5-(MeO)₃C₆H₂

Cerium(III) chloride was found to be a highly efficient reagent for the synthesis of α-aminonitriles (29) by the reaction of aldehydes (18), amines (22) and TMSCN at room temperature in excellent yields (Scheme 13).¹⁹

![Scheme 13](image_url)

R = Ph, 4-MeOC₆H₄, 2-EtOC₆H₄, 4-ClC₆H₄, 4-MeC₆H₄, 2-Furyl, 4-NCC₆H₄, 2-(CH₃)₂C, CH₃(CH₂)₄

The smooth alkylation of substituted indoles (15) with cyclopropyl ketones (30) was carried out in the presence of CeCl₃.7H₂O/LiI reagent system in refluxing under neutral conditions to produce the corresponding C-3 substituted indole derivatives (31) in good to high yields with high selectivity (Scheme 14).²⁰


Cerium(III) chloride heptahydrate catalyzed the reaction of substituted salicylaldehydes (32) with 1,3-cyclohexane diones or dimedone (33) in aqueous medium at reflux temperature to afford the corresponding 1-oxo-1,2,3,4,9,10-hexahydroxanthene derivatives (34) in high yields (Scheme 15).

Glycerin and CeCl$_3$.7H$_2$O were successfully used as recyclable catalytic system for the synthesis of several bis(indolyl)methanes (36) in good to excellent yields through the reaction of indoles (35) with aldehydes (18) (Scheme 16).

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**Scheme 14**

**Scheme 15**

**Scheme 16**
Anhydrous CeCl$_3$ was successfully used as catalyst for the synthesis of several 3-propargyl indoles (39) in good yields through the reaction of indoles (37) with propargyl alcohols (38) in nitromethane (Scheme 17).$^{23}$

\[
\begin{align*}
\text{(37)} & \quad \text{X}^1 = \text{H, Br, Cl, MeO}; \quad \text{X}^2 = \text{H, MeO}; \quad \text{X}^3 = \text{H, CH}_3 \\
\text{(38)} & \quad \text{R}^1 = \text{CH}_3, \ \text{C}_6\text{H}_5, \ \text{4-ClC}_6\text{H}_4, \ \text{4-MeOC}_6\text{H}_4; \quad \text{R}^2 = \text{CH}_3; \quad \text{R}^3 = \text{C}_6\text{H}_5, \ \text{CH}_3(\text{CH}_2)_3
\end{align*}
\]

**Scheme 17**

CeCl$_3$.7H$_2$O was found to be an efficient catalyst in the one pot reductive animation of cinnamaldehyde (40) with aromatic amines (22) for the synthesis of corresponding N-cinnamyl anilines in good yields (41) (Scheme 18).$^{24}$

\[
\begin{align*}
\text{(40)} & \quad \text{(22)} & \quad \text{(41)} \\
\text{R} = \text{C}_6\text{H}_5, \ 3-\text{O}_2\text{NC}_6\text{H}_4, \ 4-\text{MeOC}_6\text{H}_4, \ 4-\text{ClC}_6\text{H}_4, \ 4-\text{H}_3\text{CC}_6\text{H}_4
\end{align*}
\]

**Scheme 18**
MANNICH REACTION

The aminoalkylation of CH-acidic compounds was described by several authors as early as the 19th century. However, it was Carl Mannich who was first to recognize the enormous significance of this reaction type, and it was he who extended the chemistry into a broad based synthetic methodology through systematic research. Since then, this reaction that now carries his name has been developed into one of the most important C-C bond-forming reactions in organic chemistry.\textsuperscript{25,26}

The classical intermolecular Mannich Reaction is however, plagued by a number of serious disadvantages.\textsuperscript{26} Due to drastic reaction conditions and the long reaction times, unwanted side reactions often take place. Major problems are domination and the formation of methylene bisketones (42). If one uses a primary amine or ammonia as the amine component, reaction can continue until all the H atoms on the nitrogen are replaced. As a consequence, one obtains, in addition to the desired product, the other Mannich bases (43) and (44) as major components. Ketones with two reactive $\beta$-positions must be used in large excess, in order to avoid the production of bis-Mannich bases (45).

\begin{align*}
\text{R}_1 & \text{R}_2 \\
\text{O} & \text{O} \\
\text{R}_1 & \text{R}_2 \\
\text{N} & \text{R}_2 \\
\text{O} & \text{R}_1 \\
\text{R}_1 & \text{R}_2 \\
\text{N} & \text{R}_2 \\
\text{O} & \text{R}_1 \\
\text{R}_1 & \text{R}_2 \\
\text{O} & \text{NR}_2 \\
\end{align*}

(42)  (43)  (44)  (45)
The serious limitations of the classical Mannich reaction on the one hand and the versatility of β-amino carbonyl compounds on the other hand have led to the search for significantly simpler synthetic methodologies. The key to success is the use of preformed Mannich reagents. In comparison to the classical Mannich conditions, these preformed reagents guarantee a higher concentration of the electrophile, leading to lower reaction temperatures in shorter times. As a consequence, many undesired side reactions, which so often cause problems in the Mannich reaction are avoided, even with sensitive substrates.26

The acid-catalyzed Mannich reaction of substituted acetophenones (46) with aldehydes (18) and aromatic amines (22) was achieved to give the 1,3-diaryl-3-(arylamino)propanones (47) in high yield (Scheme 19).27

![Scheme 19](image)

R = H, 4-Cl, 4-Br; R¹ = C₆H₅, 4-MeOC₆H₄
R² = 4-ClC₆H₄, 4-BrC₆H₄, 4-MeC₆H₄, 4-ICH₄, 4-O₂NC₆H₄, 3-ClC₆H₄, 3-O₂NC₆H₄

In a variation of the Mannich reaction, an acid-promoted rearrangement of the azide to an iminium species (50) could occur, mostly with benzylic azides (48), the iminium species could then be trapped by the enol of the carbonyl compound (49) (Scheme 20).28

![Scheme 20](image)

R¹ = H (classical Schmidt reaction)
R² = Alkyl (Schmidt reaction of alkyl azides)
A regioselective aminomethylation of 2,4-dihydroxybenzoyl compounds (51) at the C(3) position was accomplished through a Mannich reaction of phenolic substrates with formaldehyde (52) and secondary amines (53) in methanol to yield the 3-aminomethylated derivatives (54) (Scheme 21).29

\[
\begin{align*}
R & = \text{H, Me, MeO} ; R^1 = R^2 = \text{Et, HN} \quad \text{R} \\
R^1 & = \text{R}^2 = \text{Et, HN} \\
\end{align*}
\]

Scheme 21

The Mannich reaction for the synthesis of propargylamines (56) from terminal alkynes (55), formaldehyde (52) and secondary amines (53) was carried out at room temperature in the presence of CuCl on alumina (Al\(_2\)O\(_3\)) without any organic solvent as reaction medium under microwave irradiation (Scheme 22).30

\[
\begin{align*}
R & = \text{Ph, PhMeNCH}_2, \text{1-Naphthyl-OCH}_2 \\
R^1 & = R^2 = \text{Et, Bu, CH}_2\text{Ph, MePh, i-Pr, Piperidine, Morpholine, Pyrrolidine} \\
\end{align*}
\]

Scheme 22

Three-component Mannich-type reactions of aliphatic and aromatic aldehydes (18), amines (57) and various silicon enolates (58) were efficiently catalyzed by hydrophobic polystyrene-supported sulfonic acid (PS-SO\(_3\)H) in water to afford the desired products (59) under mild conditions (Scheme 23).31
The Mannich-type reaction of imines (60) with (1-methoxy-2-methylpropenyloxy) trimethylsilane (61) was carried out in ScCO₂ in the presence of lithium heptadecafluorooctaneculfonate offered a way to synthesize β-amino carbonyl compounds (62) under environmentally benign conditions (Scheme 24).³²

A new class of artificial anthracene-fused proline catalyst (65) was used to catalyze the asymmetric three-component Mannich reactions between aldehydes (18), ketones (63), and amine (64) to afford the desired products (66) at room temperature (Scheme 25).³³
Bronsted acidic ionic liquid containing nucleophile 1-methylimidazole and triphenylphosphine with 1,4-butane sultone and inorganic anions p-toluenesulfonic acid (PTSA) and trifluoroacetic acid (TFA) catalyzed the Mannich reaction smoothly to afford β-amino carbonyl compounds (69) of acetophenone (27), aniline (67) and benzaldehyde (68) in excellent yield and less time (Scheme 26). \(^{34}\)

![Scheme 26](image)

The task-specific room-temperature ionic liquid (TSIL), \(N,N,N\)-trimethyl-\(N\)-butanesulfonic acid ammonium hydrogen sulfate \([\text{TMBSA}]\text{HSO}_4\) was synthesized as a cheap and recyclable catalyst for one-pot three-component (70, 71 & 72) Mannich reaction in water. The products (73) could simply be separated from the catalyst/water and the catalyst could be reused for atleast 7 times without any noticeable decrease in the catalytic activity (Scheme 27). \(^{35}\)

![Scheme 27](image)

\(R^1 = \text{H, 4-OCH}_3, 4-\text{NO}_2; R^2 = \text{H, 4-CH}_3, 4-\text{Cl, 4-NO}_2\)

\(R^3 = \text{C}_6\text{H}_5, (\text{CH}_2)_2\text{CO, n-C}_3\text{H}_7, 4-\text{CH}_3\text{OC}_6\text{H}_4\)
A siloxy-L-serine organocatalyst was developed to catalyze the asymmetric three-component (74, 75 & 64) Mannich reaction in the presence of water via a biphasic system, furnishing the Mannich products (76) in good yields and high enantioselectivities (Scheme 28).\(^{36}\)

\[
\begin{align*}
\text{O} & \quad \text{CHO} & \quad \text{NH}_2 & \quad \text{TBDPSO} & \quad \text{COOH} \\
\text{O} & \quad \text{NO}_2 & \quad \text{NH}_2 & \quad \text{H}_2\text{O, rt} \\
\text{(74)} & \quad \text{(75)} & \quad \text{(64)} & \quad \text{(76)}
\end{align*}
\]

Scheme 28

Ceric ammonium nitrate (CAN) in PEG was used as an efficient and recyclable solvent system for the one pot, three component Mannich reaction of acetophenone (27) with aromatic aldehydes (70), and aromatic amines (71) to give the \(\beta\)-amino carbonyl compounds in high yields (77) (Scheme 29).\(^{37}\)

\[
\begin{align*}
\text{O} & \quad \text{CHO} & \quad \text{NH}_2 & \quad \text{CH}_3 & \quad \text{R}^1 \\
\text{O} & \quad \text{NO}_2 & \quad \text{NH}_2 & \quad \text{H}_2\text{O, rt} & \quad \text{PEG, 45 }^\circ\text{C} \\
\text{(27)} & \quad \text{(70)} & \quad \text{(71)} & \quad \text{(77)}
\end{align*}
\]

\(R = \text{H, 4-CH}_3, 4-\text{OCH}_3, 4-\text{NO}_2, 4-\text{Br}; R^1 = \text{H, CH}_3, 3,4-(\text{CH}_3)_2, 4-\text{Cl, 4-OCH}_3, 4-\text{NO}_2, 2-\text{NO}_2\)

Scheme 29

Recyclable heterogeneous Cu-nanoparticles efficiently catalyzed the one-pot three-component Mannich reaction of aromatic ketones (72) or cyclohexanone (74), aromatic aldehydes (70) and amines (22) in methanol to afford the \(\beta\)-amino carbonyl compounds (78 & 79) (Scheme 30).\(^{38}\)
Trypsin-catalyzed three-component Mannich reaction of aromatic aldehydes (18), aromatic amines (22) and acetone (80) was reported for the synthesis of β-amino carbonyl compounds (81) with moderate to excellent yields (Scheme 31).39

Iodine-alumina was employed as a catalyst in the coupling reactions of aldehydes (18), enolizable ketones (72) or 1,3-dicarbonyls with methyl carbamate (82) or aromatic amines (22) under microwave irradiation to afford β-amino carbonyl compounds (83 & 84) in excellent yields (Scheme 32).40
A simple and eco-friendly method for the aminomethylation of various 3-substituted oxindoles (85) with dibutylamine (86) and formalin (87) via three component Mannich reaction in aqueous media was established for the synthesis of desired aminomethylated products (88) in good yields (Scheme 33).\(^{41}\)

Scheme 32

Scheme 33
OBJECT OF THE PRESENT WORK

Three-component reactions have emerged as a useful method, since the combination of three-components to generate new products in a single step is extremely economical, among the multi-component reaction. Our research group focuses on finding efficient chemical transformation using three or more components in a single step by a catalytic process since it avoids the use of stoichiometric toxic reagents, large amounts of solvents and expensive purification techniques which is also the fundamental targets of modern organic synthesis.

There are many types of three-component reaction reported in the literature and Mannich reaction is one of the most important C-C bonds forming reaction. Basically, Mannich reaction is the synthesis of β-amino carbonyl compounds and as such is one of the most important reaction in organic synthesis. The gaining impetus of the Mannich reaction has been fuelled by the ubiquitous nature of nitrogen containing compounds in drugs and natural products. However, the classical Mannich reaction was plagued by a number of serious disadvantages with limited applications. Therefore, numerous modern versions of Mannich reaction have been developed to overcome the negative aspect of this classical method. In general, improved methodologies rely on two-component system using preformed electrophiles such as imines and stable nucleophiles such as enolates, enols, ethers and enamines, but the preferable route is the use of a one-pot three-component strategy as it facilitates wide range of structural variations, but these early three-component reactions were hampered due to a number of serious limitations.

The conventional catalyst for the synthesis of β-amino carbonyl compounds of aldehydes, ketones and amines involve mainly organic and mineral acids like proline, acetic acid, p-dodecyl benzene sulfonic acid and other Lewis
acids.\textsuperscript{62,63} They often suffer the drawbacks of long reaction times, harsh reaction conditions, toxicity and difficulty in product isolation. While searching for economical and better catalyst, we thought its worthwhile to perform a controlled reaction for one-pot three-component Mannich reaction catalyzed by cerium(III) chloride heptahydrate (CeCl\textsubscript{3}.7H\textsubscript{2}O), which has attracted considerable attention because of its diverse application as a promoter in organic synthesis.\textsuperscript{64}

Cerium halides are relatively an effective Lewis acid catalyst\textsuperscript{65}, as it is water tolerant, non-toxic, easy to handle, inexpensive and can be reused without further purification. In this work, we have found CeCl\textsubscript{3}.7H\textsubscript{2}O as an efficient catalyst for the synthesis of $\beta$-amino carbonyl compounds (92a) at room temperature through a one-pot three-component reaction of acetophenone (89) aromatic aldehydes (90) and aromatic amines (91) in methanol (Scheme 34). It is also noteworthy to mention that our environmentally benign reaction does not generate any toxic waste products.
RESULTS AND DISCUSSION

In order to verify the efficient catalytic behavior of CeCl₃·7H₂O, a controlled reaction was performed using benzaldehyde (1 mmol), aniline (1 mmol) and acetophenone (1 mmol) in methanol (5 mL) at room temperature. In the absence of CeCl₃·7H₂O, the reaction resulted in the formation of a fused product after 8 h at 50 °C (10% yields). However, under same condition by employing 1 mol% of CeCl₃·7H₂O, the reaction afforded expected products up to 85% yield within 4 h of reaction time.

With this optimistic result in hand, we further investigated the best reaction conditions by using different amounts of CeCl₃·7H₂O. An increase in the quantity of CeCl₃·7H₂O from 1 mol% to 3 mol% not only decreased the reaction time from 4 h to 2 h but also increased the product yield slightly from 85% to 93%. Thus the use of 3 mol% CeCl₃·7H₂O is sufficient to push the reaction forward for the optimum yield of β-amino carbonyl compounds (Table 1).

Further, we have also scrutinized this reaction by employing various Lewis acids such as CuSO₄, CeCl₃·7H₂O, CuCl₂, ZnCl₂, and AlCl₃ and we found that CeCl₃·7H₂O showed the best result among all the catalysts (Table 2, Entry 2). Remarkably, catalyst with high Lewis acidity such as ZnCl₂ and AlCl₃ failed to catalyze the reaction efficiently and resulted in lower yields of the corresponding product (Table 2).

A possible mechanism of CeCl₃·7H₂O catalyzed Mannich reaction is shown in scheme 35. The role of catalyst is the activation of precursors through coordination leading the desired product in good yield with less reaction time. First it coordinates with the carbonyl oxygen of aldehyde and activating it, and then nucleophilic attack by amine gives (I) which in turns gets converted to intermediate imine (II) after
dehydration. The intermediate (II) again activated by the catalyst through coordination by CeCl₃ and then the attack by enol to imine gives the desired product (92a).

Encouraged by these remarkable results, we screened a variety of aromatic aldehydes and amines having electron-withdrawing as well as electron-donating groups and in each case we observed good to excellent yields, however, when ortho-substituted anilines were used as substrates, the reaction gave no product probably due to steric hindrance of ortho-substituents. In the investigation of various substituted benzaldehydes, it was found that p-methylbenzaldehyde is the most reactive substrate in the reaction (Table 3, Entry 92c). It was observed that the catalyst had no catalytic activity for the reactions when aliphatic aldehydes and amines were used as substrate.

In order to ascertain the scope and limitation of this CeCl₃.7H₂O catalyzed Mannich reaction, we have also extended the use of this catalytic systems to the reaction of cyclohexanone with various aldehydes and amines as depicted in Table 3. Cyclohexanone showed antiselectivities determined by ¹H NMR analysis of crude products.

Moreover, we also examined the role of the solvents for Mannich reaction. Various solvents were employed in order to evaluate the scope and limitations of this reaction. We rationalized that the yield of the reaction would be faster for protic solvents rather than aprotic solvents. After screening different solvents, it was found that CeCl₃.7H₂O catalyzed synthesis of β-amino carbonyl compounds were not only faster, but also resulted in good yields in protic solvents such as MeOH as compared to other solvents (Table 4). It is interesting to note that the yield of the products is comparatively low in the case of polar aprotic solvents such as DMSO and DMF.
Clearly, methanol stands out as the solvent of choice, with fast conversion and quantitative yield of the products. Furthermore, under solvent free condition the conversion rates were found to be negligible (Table 4).

Mannich reaction was very sensitive to reaction temperature. The high temperature could improve the reaction rate and shorten the reaction time, but favor side reactions and the oxygenolysis of aldehyde and amine. In our investigation for the effect of temperature, we found that CeCl$_3$.7H$_2$O efficiently catalyzed the Mannich reaction at room temperature.
Scheme 34: CeCl$_3$.7H$_2$O-catalyzed Mannich reaction.

Scheme 35: Proposed mechanism of CeCl$_3$.7H$_2$O catalyzed Mannich reaction.
EXPERIMENTAL

In a 50 mL round bottom flask, acetophenone (1 mmol), aromatic aldehydes (1 mmol) and aromatic amines (1 mmol) in MeOH (5 mL) were mixed and stirred at room temperature. To this, CeCl$_3$.7H$_2$O (cerium chloride heptahydrate) (3 mol%) was added. The progress of reaction mixture was monitored by TLC (using Petroleum Ether/AcOEt = 80:20 as an eluent). After completion of the reaction, the solid product was collected by filtration at pump and washed with methanol and water. The crude product was subjected to purification by recrystallization using ethanol, was subjected to further purification by silica gel column chromatography using 15% ethyl acetate, and 85% petroleum ether as an eluent to yield the β-amino carbonyl compounds. The structures of all the products were unambiguously established on the basis of their spectral analysis (IR, $^1$H NMR, $^{13}$C NMR and mass spectral data). All the products are known compounds.
Table 1: Optimization of the concentration of CeCl$_3$·7H$_2$O in the Mannich reaction.$^a$

<table>
<thead>
<tr>
<th>Entry</th>
<th>CeCl$_3$·7H$_2$O (mol%)</th>
<th>Time (h)</th>
<th>Yield (%)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>4</td>
<td>85</td>
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<tr>
<td>3</td>
<td>2</td>
<td>2</td>
<td>90</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>2</td>
<td>93</td>
</tr>
</tbody>
</table>

$^a$Reaction conditions: acetophenone (1 mmol), benzaldehyde (1 mmol) and aniline (1 mmol), catalyst CeCl$_3$·7H$_2$O (x mol%); solvent methanol (5 mL); rt.

$^b$Isolated yields.

Table 2: Optimization of various Lewis acids for the Mannich reaction.$^a$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Time (h)</th>
<th>Yield (%)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CuSO$_4$</td>
<td>2</td>
<td>55</td>
</tr>
<tr>
<td>2</td>
<td>CeCl$_3$·7H$_2$O</td>
<td>2</td>
<td>93</td>
</tr>
<tr>
<td>3</td>
<td>CuCl$_2$</td>
<td>2</td>
<td>40</td>
</tr>
<tr>
<td>4</td>
<td>ZnCl$_2$</td>
<td>2</td>
<td>15</td>
</tr>
<tr>
<td>5</td>
<td>AlCl$_3$</td>
<td>2</td>
<td>12</td>
</tr>
</tbody>
</table>

$^a$Reaction conditions: acetophenone (1 mmol), benzaldehyde (1 mmol) and aniline (1 mmol), catalyst x (3 mol%); solvent methanol (5 mL); rt.

$^b$Isolated yields.
Table 3: Synthesis of various β-amino carbonyls using CeCl$_3$.7H$_2$O.$^a$

\[
\begin{align*}
\text{R}^\text{Me}O & + R^1\text{CHO} + R^2\text{NH}_2 \xrightarrow{\text{CeCl}_3$.7H}_2\text{O (3 mol\%)} \text{MeOH, rt} \text{R}^\text{O}R^1\text{NHR}^2
\end{align*}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ketone</th>
<th>$R^1$</th>
<th>$R^2$</th>
<th>Time (h)</th>
<th>Yield (%)$^b$</th>
<th>Mp (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>92a</td>
<td>Acetophenone</td>
<td>Ph</td>
<td>4-MeC$_6$H$_4$</td>
<td>2.5</td>
<td>96</td>
<td>164-167</td>
</tr>
<tr>
<td>92b</td>
<td>Acetophenone</td>
<td>Ph</td>
<td>Ph</td>
<td>2</td>
<td>93</td>
<td>168-170</td>
</tr>
<tr>
<td>92c</td>
<td>Acetophenone</td>
<td>4-MeC$_6$H$_4$</td>
<td>Ph</td>
<td>2.5</td>
<td>97</td>
<td>129-130</td>
</tr>
<tr>
<td>92d</td>
<td>Acetophenone</td>
<td>Ph</td>
<td>4-MeOC$_6$H$_4$</td>
<td>3</td>
<td>91</td>
<td>162-163</td>
</tr>
<tr>
<td>92e</td>
<td>Acetophenone</td>
<td>Ph</td>
<td>4-O$_2$NC$_6$H$_4$</td>
<td>8</td>
<td>73</td>
<td>184-185</td>
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<tr>
<td>92f</td>
<td>Acetophenone</td>
<td>Ph</td>
<td>4-ClC$_6$H$_4$</td>
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<td>95</td>
<td>172-173</td>
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<td>92</td>
<td>145-146</td>
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<tr>
<td>92h</td>
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<td>Ph</td>
<td>3</td>
<td>91</td>
<td>135-137</td>
</tr>
<tr>
<td>92i</td>
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<td>Ph</td>
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<td>74</td>
<td>103-104</td>
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<tr>
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<td>4-MeOC$_6$H$_4$</td>
<td>4-IC$_6$H$_4$</td>
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<td>76</td>
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<td>Cyclohexanone</td>
<td>4-MeOC$_6$H$_4$</td>
<td>Ph</td>
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<td>92r</td>
<td>Cyclohexanone</td>
<td>Ph</td>
<td>4-ClC$_6$H$_4$</td>
<td>5</td>
<td>91</td>
<td>137-138</td>
</tr>
</tbody>
</table>

$^a$Reaction conditions: acetophenone/cyclohexanone (1 mmol), aldehydes (1 mmol) and anilines (1 mmol), catalyst CeCl$_3$.7H$_2$O (3 mol\%); solvent methanol (5 mL); rt.

$^b$Isolated yields.
Table 4: Effect of solvent for the synthesis of β-amino carbonyls.\textsuperscript{a}

<table>
<thead>
<tr>
<th>S.N.</th>
<th>Solvent</th>
<th>Entry 2 (Table 3)</th>
<th>Entry 7 (Table 3)</th>
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</thead>
<tbody>
<tr>
<td></td>
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<td>Time (h)</td>
<td>Yield (%)\textsuperscript{b}</td>
</tr>
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<td>Ethanol</td>
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<td>92</td>
</tr>
<tr>
<td>2</td>
<td>PEG 200</td>
<td>2</td>
<td>90</td>
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<tr>
<td>3</td>
<td>Methanol</td>
<td>2</td>
<td>93</td>
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<tr>
<td>4</td>
<td>DMF</td>
<td>2</td>
<td>60</td>
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<tr>
<td>5</td>
<td>DMSO</td>
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<td>55</td>
</tr>
<tr>
<td>6</td>
<td>MeCN</td>
<td>2</td>
<td>72</td>
</tr>
<tr>
<td>7</td>
<td>Solvent-free</td>
<td>2</td>
<td>-</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Reaction conditions: acetophenone (1 mmol), aldehydes (1 mmol) and anilines (1 mmol), catalyst \( \text{CeCl}_3 \cdot 7\text{H}_2\text{O} \) (3 mol%); different solvents (5 mL); rt.

\textsuperscript{b}Isolated yields.
Spectroscopic data of synthesized β-amino carbonyl compounds (92a-r)

1,3-Diphenyl-3-p-tolylamino-propan-1-one (92a): White Solid; RF = 0.70
(Petroleum Ether/ AcOEt = 80:20); IR (KBr/cm⁻¹): νmax = 3383, 1698; ¹H NMR (CDCl₃, TMS, 300 MHz): δ = 2.47 (s, 3H, -CH₃), 3.45-3.62 (m, 2H), 4.47 (t, 1H), 6.91 (d, J = 8.5 Hz, 2H, Ar-H), 6.97 (d, J = 7.9 Hz, 2H, Ar-H), 7.03-7.07 (m, 2H, Ar-H), 7.15 (d, J = 6.3 Hz, 2H, Ar-H), 7.28-7.32 (m, 1H, Ar-H), 7.46-7.49 (m, 2H, Ar-H), 7.66-7.69 (m, 1H, Ar-H), 7.83 (d, J = 7.9 Hz, 2H, Ar-H); ¹³C NMR (CDCl₃, 75 MHz): δ = 21.3, 45.5, 56.7, 113.1, 120.5, 122.5, 128.9, 128.3, 130.4, 133.1, 135.3, 144.6, 196.6; m/z 313.362 (M⁺).

1,3-Diphenyl-3-phenylamino-propan-1-one (92b): White Solid; RF = 0.68
(Petroleum Ether/ AcOEt = 80:20); IR (KBr/cm⁻¹): νmax = 3386, 1671; ¹H NMR (CDCl₃, TMS, 300 MHz): δ = 3.32-3.47 (m, 2H), 4.98 (t, 1H), 6.51 (d, J = 8.0 Hz, 2H, Ar-H), 6.63-6.69 (m, 1H, Ar-H). 7.00-7.04 (m, 2H, Ar-H), 7.20 (d, J = 6.5 Hz, 2H, Ar-H), 7.23-7.26 (m, 1H, Ar-H), 7.38-7.41 (m, 2H, Ar-H), 7.45-7.51 (m, 1H, Ar-H), 7.53-7.57 (m, 2H, Ar-H), 7.84 (d, J = 7.8 Hz, 2H, Ar-H); ¹³C NMR (CDCl₃, 75 MHz): δ = 46.3, 54.2, 115.3, 119.4, 126.4, 128.6, 128.8, 129.5, 132.3, 135.8, 146.2, 197.0; m/z 301.368 (M⁺).

1-Phenyl-3-phenylamino-3-p-tolyl-propan-1-one (92c): White Solid; RF = 0.61
(Petroleum Ether/ AcOEt = 80:20); IR (KBr/cm⁻¹): νmax = 3387, 1667; ¹H NMR (CDCl₃, TMS, 300 MHz): δ = 2.27 (s, 3H, -CH₃), 3.31-3.45 (m, 2H), 4.82 (t, 1H), 6.75 (d, J = 8.1 Hz, 2H, Ar-H), 6.83-6.91 (m, 1H, Ar-H), 7.04-7.08 (m, 2H, Ar-H), 7.10 (d, J = 7.8 Hz, 2H, Ar-H), 7.21 (d, J = 7.38-7.27 Hz, 2H, Ar-H), 7.36-7.41 (m, 2H, Ar-H), 7.41-7.49 (m, 1H, Ar-H), 7.89 (d, J = 8.1 Hz, 2H, Ar-H); ¹³C NMR (CDCl₃, 75 MHz): δ = 21.7, 42.7, 54.5, 111.4, 119.5, 123.6, 127.4, 128.6, 131.9, 132.3, 135.4, 143.2, 190.6; m/z 317.402 (M⁺).
3-(4-Methoxy-phenylamino)-1,3-diphenyl-propan-1-one (92d): White Solid; $R_f = 0.64$ (Petroleum Ether/ AcOEt = 80:20); IR (KBr/cm$^{-1}$): $\nu_{max} = 3385, 1675$; $^1$H NMR (CDCl$_3$, TMS, 300 MHz): $\delta = 3.39-3.44$ (m, 2H), 3.58 (s, 3H, -OCH$_3$), 4.86 (t, 1H), 6.51 (d, $J = 8.6$ Hz, 2H, Ar-H), 6.71 (d, $J = 8.9$, 2H, Ar-H), 6.96-7.05 (m, 1H, Ar-H), 7.15 (d, $J = 8.3$ Hz, 2H, Ar-H), 7.24-7.30 (m, 2H, Ar-H), 7.38-7.41 (m, 2H, Ar-H), 7.33-7.53 (m, 1H, Ar-H), 7.81 (d, $J = 7.5$ Hz, 2H, Ar-H); $^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta = 46.2, 55.3, 58.2, 115.2, 122.7, 126.2, 127.1, 128.6, 128.8, 128.9, 129.3, 132.5, 138.5, 141.7, 1510.2, 195.6; m/z 332.473 (M$^+$).

3-(4-Nitro-phenylamino)-1,3-diphenyl-propan-1-one (92e): White Solid; $R_f = 0.48$ (Petroleum Ether/ AcOEt = 80:20); IR (KBr/cm$^{-1}$): $\nu_{max} = 3364, 1627$; $^1$H NMR (CDCl$_3$, TMS, 300 MHz): $\delta = 3.67$ (d, $J = 6.8$ Hz, 2H), 5.12 (t, 1H), 6.37 (brs, 2H, Ar-H), 6.64 (d, $J = 6.4$ Hz, 2H, Ar-H), 7.20-7.24 (m, 1H, Ar-H), 7.29-7.38 (m, 2H, Ar-H), 7.37 (d, $J = 7.7$ Hz, 2H, Ar-H), 7.59-7.67 (m, 1H, Ar-H), 8.01 (d, $J = 7.2$ Hz, 2H, Ar-H); $^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta = 45.2, 53.1, 111.7, 125.9, 126.1, 127.4, 128.9, 128.1, 130.5, 132.8, 136.7, 138.6, 140.0, 197.8; m/z 348.637 (M$^+$).

3-(4-Chloro-phenylamino)-1,3-diphenyl-propan-1-one (92f): White Solid; $R_f = 0.79$ (Petroleum Ether/ AcOEt = 80:20); IR (KBr/cm$^{-1}$): $\nu_{max} = 3325, 1654$; $^1$H NMR (CDCl$_3$, TMS, 300 MHz): $\delta = 3.37-3.54$ (m, 2H), 4.91 (t, 1H), 6.35 (d, $J = 8.4$ Hz, 2H, Ar-H), 6.68 (d, $J = 8.1$ Hz, 2H, Ar-H), 7.11 (d, $J = 6.6$ Hz, 2H, Ar-H), 7.22-7.28 (m, 2H, Ar-H), 7.31-7.34 (m, 2H, Ar-H), 7.38-7.42 (m, 2H, Ar-H), 7.47-.51 (m, 1H, Ar- H), 7.86 (d, $J = 7.8$ Hz, 2H, Ar-H); $^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta = 44.08, 55.1, 116.4, 122.5, 125.7, 127.3, 128.4, 128.7, 129.3, 133.6, 137.5, 140.6, 197.4; m/z 335.832 (M$^+$).

3-(3,4-Dimethyl-phenylamino)-1,3-diphenyl-propan-1-one (92g): White Solid; $R_f = 0.73$ (Petroleum Ether/ AcOEt = 80:20); IR (KBr/cm$^{-1}$): $\nu_{max} = 3410, 1702$; $^1$H
NMR (CDCl<sub>3</sub>, TMS, 300 MHz): δ = 2.35 (s, 6H, -CH<sub>3</sub>), 3.10 (d, <i>J</i> = 6.1 Hz, 2H), 4.56 (t, 1H), 6.28 (s, 1H, Ar-H), 6.29 (d, <i>J</i> = 6.8 Hz, 2H, Ar-H), 6.65 (d, <i>J</i> = 8.1 Hz, 2H, Ar-H), 7.05-7.11 (m, 1H, Ar-H), 7.28 (d, <i>J</i> = 6.7 Hz, 2H, Ar-H), 7.28-7.31 (m, 2H, Ar-H), 7.30-7.34 (m, 2H, Ar-H), 7.42-7.49 (m, 1H, Ar-H), 7.93 (d, <i>J</i> = 7.8 Hz, 2H, Ar-H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz): δ = 17.3, 42.4, 55.7, 115.4, 123.2, 126.5, 128.6, 128.7, 129.7, 129.8, 131.3, 137.4, 141.4, 192.5; m/z 327.432 (M<sup>+</sup>).

3-(4-Methoxy-phenyl)-1-phenyl-3-phenylamino-propan-1-one (92h): White Solid; <i>R</i><sub>f</sub> = 0.67 (Petroleum Ether/ AcOEt = 80:20); IR (KBr/cm<sup>-1</sup>): <i>ν</i><sub>max</sub> = 3401, 1679; <sup>1</sup>H NMR (CDCl<sub>3</sub>, TMS, 300 MHz): δ = 3.40-3.47 (m, 2H), 3.62 (s, 3H, -OCH<sub>3</sub>), 4.96 (t, 1H), 6.47 (d, <i>J</i> = 8.1 Hz, 2H, Ar-H), 6.52 (t, 1H, Ar-H), 6.86-6.90 (m, 2H, Ar-H), 7.23 (d, <i>J</i> = 8.2 Hz, 2H, Ar-H), 7.28-7.33 (m, 2H, Ar-H), 7.41-7.44 (m, 2H, Ar-H), 7.51-7.54 (m, 1H, Ar-H), 7.89 (d, <i>J</i> = 7.5 Hz, 2H, Ar-H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz): δ = 47.6, 54.2, 56.2, 113.2, 113.9, 116.4, 128.6, 128.1, 127.9, 129.4, 132.9, 134.2, 137.7, 160.2, 198.2; m/z 331.423 (M<sup>+</sup>).

3-(4-Nitro-phenyl)-1-phenyl-3-phenylamino-propan-1-one (92i): White Solid; <i>R</i><sub>f</sub> = 0.54 (Petroleum Ether/ AcOEt = 80:20); IR (KBr) (KBr/cm<sup>-1</sup>): <i>ν</i><sub>max</sub> = 3372, 1681; <sup>1</sup>H NMR (CDCl<sub>3</sub>, TMS, 300 MHz): δ = 3.52 (d, <i>J</i> = 6.1 Hz, 2H), 5.13 (t, 1H), 6.52 (d, <i>J</i> = 6.5 Hz, 2H, Ar-H), 6.66-6.70 (m, 1H, Ar-H), 7.07-7.11 (m, 2H, Ar-H), 7.43-7.48 (m, 2H, Ar-H), 7.55-7.59 (m, 2H, Ar-H), 7.65 (d, <i>J</i> = 7.5 Hz, 2H, Ar-H), 7.87 (d, <i>J</i> = 8.0 Hz, 2H, Ar-H), 8.16 (d, <i>J</i> = 9.6 Hz, 2H, Ar-H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz): δ = 46.4, 54.1, 112.8, 116.8, 123.4, 128.2, 128.4, 128.6, 129.3, 132.6, 137.6, 140.2, 143.6, 146.4, 198.4; m/z 346.381 (M<sup>+</sup>).

3-(4-Bromo-phenyl)-1-phenyl-3-phenylamino-propan-1-one (92j): White Solid; <i>R</i><sub>f</sub> = 0.59 (Petroleum Ether/ AcOEt = 80:20); IR (KBr/cm<sup>-1</sup>): <i>ν</i><sub>max</sub> = 3385, 1670; <sup>1</sup>H NMR (CDCl<sub>3</sub>, TMS, 300 MHz): δ = 3.41 (d, <i>J</i> = 5.6, 2H), 3.69 (s, 3H, -OCH<sub>3</sub>), 4.91...
(t, 1H), 6.48 (d, J = 7.6 Hz, 2H, Ar-H), 6.70 (d, J = 6.9 Hz, 2H, Ar-H), 7.04 (d, J = 6.7 Hz, 2H, Ar-H), 7.33 (d, J = 7.6 Hz, 2H, Ar-H), 7.41-7.46 (m, 2H, Ar-H), 7.54-7.58 (m, 1H, Ar-H), 7.90 (d, J = 6.7 Hz, 2H, Ar-H); ¹³C NMR (CDCl₃, 75 MHz): δ = 47.2, 54.4, 56.8, 112.8, 113.9, 86.8, 127.8, 128.3, 128.1, 138.6, 132.9, 134.2, 137.7, 160.7, 197.8; m/z 457.348 (M⁺).

3-(4-Chloro-phenyl)-1-phenyl-3-phenylamino-propan-1-one (92k): White Solid; Rf = 0.70 (Petroleum Ether/ AcOEt = 80:20); IR (KBr/cm⁻¹): νmax = 3382, 1690; ¹H NMR (CDCl₃, TMS, 300 MHz): δ = 3.48 (d, J = 5.8 Hz, 2H), 5.18 (t, 1H), 6.60 (d, J = 6.2 Hz, 2H, Ar-H), 6.68-6.73 (m, 1H, Ar-H), 7.07-7.12 (m, 2H, Ar-H), 7.28 (d, J = 6.6 Hz, 2H, Ar-H), 7.52 (d, J = 8.1 Hz, 2H, Ar-H), 7.60-7.67 (m, 2H, Ar-H), 7.71-7.76 (m, 1H, Ar-H), 7.96 (d, J = 9.1 Hz, 2H, Ar-H); ¹³C NMR (CDCl₃, 75 MHz): δ = 47.9, 53.7, 111.5, 115.3, 128.1, 128.6, 128.7, 128.9, 129.6, 131.8, 136.5, 141.1, 144.5, 196.6; m/z 337.416 (M⁺).

3-(4-Iodo-phenylamino)-1,3-diphenyl-propan-1-one (92l): White Solid; Rf = 0.63 (Petroleum Ether/ AcOEt = 80:20); IR (KBr/cm⁻¹): νmax = 3383, 1669; ¹H NMR (CDCl₃, TMS, 300 MHz): δ = 3.34 (m, 2H), 4.64 (t, 1H), 6.24 (d, J = 7.0 Hz, 2H, Ar-H), 6.96 (d, J = 8.1 Hz, 2H, Ar-H), 7.02-7.06 (m, 1H, Ar-H), 7.10-7.14 (m, 2H, Ar-H), 7.25 (d, J = 6.3 Hz, 2H, Ar-H), 7.29-7.34 (m, 2H, Ar-H), 7.42-7.45 (m, 1H, Ar-H), 7.83 (d, J = 8.1 Hz, 2H, Ar-H); ¹³C NMR (CDCl₃, 75 MHz): δ = 46.4, 55.3, 113.2, 126.2, 126.4, 127.8, 128.5, 128.7, 128.9, 132.3, 132.5, 137.5, 138.8, 142.8, 198.2; m/z 346.382 (M⁺).

3-Phenyl-3-phenylamino-1-p-tolyl-propan-1-one (92m): White Solid; Rf = 0.74 (Petroleum Ether/ AcOEt = 80:20); IR (KBr/cm⁻¹): νmax = 3380, 1670; ¹H NMR (CDCl₃, TMS, 300 MHz): δ = 2.42 (s, 3H, -CH₃), 3.45 (d, J = 5.9 Hz, 2H), 4.93 (t, 1H), 6.43 (d, J = 7.8 Hz, 2H, Ar-H), 6.58 (m, 1H, Ar-H). 6.98 (m, 2H, Ar-H), 7.11
Chapter IV A

(\( d, J = 6.4 \text{ Hz}, 2\text{H, Ar-H})\), 7.19-7.27 (m, 3\text{H, Ar-H}), 7.43 (\( d, J = 7.8 \text{ Hz}, 2\text{H, Ar-H})\), 7.86 (\( d, J = 7.2 \text{ Hz}, 2\text{H, Ar-H})\); \(^{13}\text{C}\) NMR (CDCl\(_3\), 75 MHz): \( \delta = 20.7, 44.2, 52.3, 109.2, 113.5, 124.2, 126.3, 127.3, 127.5, 128.1, 128.4, 131.5, 140.2, 141.7, 194.3; m/z 316.374 (M\(^+\)).

1-(4-Nitro-phenyl)-3-phenyl-3-phenylamino-propan-1-one (92n): White Solid; \( R_f = 0.49 \) (Petroleum Ether/ AcOEt = 80:20); IR (KBr/cm\(^{-1}\)): \( \nu_{max} = 3400, 1678; \) \(^1\text{H}\) NMR (CDCl\(_3\), TMS, 300 MHz): \( \delta = 3.44-3.57 \) (m, 2\text{H}), 5.10 (t, 1\text{H}), 6.48 (\( d, J = 6.2 \text{ Hz}, 2\text{H, Ar-H})\), 6.63-6.69 (m, 2\text{H, Ar-H}). 6.80-6.83 (m, 1\text{H, Ar-H}), 7.14 (\( d, J = 7.6 \text{ Hz}, 2\text{H, Ar-H})\), 7.23-7.26 (m, 1\text{H, Ar-H}), 7.31-7.35 (m, 2\text{H, Ar-H}), 7.62 (\( d, J = 6.3 \text{ Hz}, 2\text{H, Ar-H})\); 7.92 (\( d, J = 7.2 \text{ Hz}, 2\text{H, Ar-H})\); \(^{13}\text{C}\) NMR (CDCl\(_3\), 75 MHz): \( \delta = 46.2, 53.4, 110.1, 114.9, 122.7, 123.5, 126.1, 127.9, 128.3, 128.8, 142.6, 141.3, 151.8, 196.4; m/z 346.217 (M\(^+\)).

2-(Phenyl-phenylamino-methyl)-cyclohexanone (92o): White Solid; \( R_f = 0.68 \) (Petroleum Ether/ AcOEt = 80:20); IR (KBr/cm\(^{-1}\)): \( \nu_{max} = 3390, 1690; \) \(^1\text{H}\) NMR (CDCl\(_3\), TMS, 300 MHz, syn/anti = 48:52): \( \delta = 1.25-1.76 \) (m, 6\text{H}), 2.28-2.44 (m, 2\text{H}), 2.73-2.78 (m, 1\text{H}), 4.62 (\( d, J = 7.6 \text{ Hz}, 0.52\text{H})\), 4.70 (brs, 1\text{H}), 4.79 (\( d, J = 4.8 \text{ Hz}, 0.48\text{H})\), 6.37 (\( d, J = 7.3 \text{ Hz}, 2\text{H, Ar-H})\), 6.51-6.63 (m, 1\text{H, Ar-H}), 7.02-7.07 (m, 2\text{H, Ar-H}), 7.19-7.26 (m, 1\text{H, Ar-H}), 7.29-7.37 (m, 2\text{H, Ar-H}), 7.60 (\( d, J = 7.8 \text{ Hz}, 2\text{H, Ar-H})\); \(^{13}\text{C}\) NMR (CDCl\(_3\), 75 MHz): \( \delta = 23.2, 24.5, 28.3, 36.7, 52.1, 57.4, 108.6, 113.5, 123.1, 127.5, 128.9, 138.6, 140.4, 203.8; m/z 280.329 (M\(^+\)).

2-(Phenyl-p-tolylamino-methyl)-cyclohexanone (92p): White Solid; \( R_f = 0.62 \) (Petroleum Ether/ AcOEt = 80:20); IR (KBr/cm\(^{-1}\)): \( \nu_{max} = 3406, 1702; \) \(^1\text{H}\) NMR (CDCl\(_3\), TMS, 300 MHz, syn/anti = 34:66): \( \delta = 1.33-1.89 \) (m, 6\text{H}), 2.14 (s, 3\text{H, -CH3}), 2.36-2.57 (m, 2\text{H}), 2.97-3.04 (m, 1\text{H}), 4.52 (\( d, J = 5.2 \text{ Hz}, 0.34\text{H})\), 4.52 (\( d, J = 6.8 \text{ Hz}, 0.66\text{H})\), 4.77 (brs, 1\text{H}), 6.45 (\( d, J = 7.5 \text{ Hz}, 2\text{H, Ar-H})\), 6.84 (\( d, J = 8.2 \text{ Hz}, 2\text{H, Ar-H})\),
7.02-7.18 (m, 1H, Ar-H), 7.32-7.42 (m, 2H, Ar-H), 7.62 (d, \( J = 7.1 \) Hz, 2H, Ar-H);

\(^{13}\)C NMR (CDCl\(_3\), 75 MHz): \( \delta = 21.0, 23.2, 25.7, 32.9, 43.3, 55.1, 57.3, 113.3, 127.6, 126.8, 126.4, 127.1, 128.9, 140.4, 142.5, 209.2; m/z 293.106 (M\(^+\)).

2-(4-Methoxy-phenyl)-phenylamino-methyl-cyclohexanone (92q): White Solid; \( R_f = 0.69 \) (Petroleum Ether/ AcOEt = 80:20); IR (KBr/cm\(^{-1}\)): \( \nu_{max} = 3332, 1690; \) \(^{1}\)H NMR (CDCl\(_3\), TMS, 300 MHz, syn/anti = 42:58): \( \delta = 1.68-1.93 \) (m, 6H), 2.42-2.47 (m, 2H), 2.72-2.76 (m, 1H), 3.89 (s, 3H, OCH\(_3\)), 4.08 (d, \( J = 7.3 \) Hz, 0.58H), 4.63 (d, \( J = 4.4 \) Hz, 0.42H), 4.71 (br, s, 1H), 6.61-6.64 (m, 1H, Ar-H), 6.68 (d, \( J = 8.3 \) Hz, 2H, Ar-H), 7.03-7.10 (m, 2H, Ar-H), 7.16 (d, \( J = 7.6 \) Hz, 2H, Ar-H), 7.27 (d, \( J = 8.4 \) Hz, 2H, Ar-H); \(^{13}\)C NMR (CDCl\(_3\), 75 MHz): \( \delta = 20.8, 23.2, 27.8, 30.9, 41.3, 57.2, 56.3, 113.1, 117.2, 126.8, 128.6, 128.8, 136.4, 138.2, 147.0, 212.7; m/z 309.615 (M\(^+\)).

2-(4-Chloro-phenylamino)-phenyl-methyl-cyclohexanone (92r): Yellowish solid; \( R_f = 0.73 \) (Petroleum Ether/ AcOEt = 80:20); IR (KBr/cm\(^{-1}\)): \( \nu_{max} = 3378, 1674; \) \(^{1}\)H NMR (CDCl\(_3\), TMS, 300 MHz, syn/anti = 28:72): \( \delta = 1.60-1.92 \) (m, 6H), 2.28-2.31 (m, 2H), 2.61-2.65 (m, 1H), 4.10 (d, \( J = 8.2 \) Hz, 0.72H), 4.30 (d, \( J = 4.1 \) Hz, 0.28H), 4.56 (brs, 1H), 6.58 (d, \( J = 7.3 \) Hz, 2H, Ar-H), 6.98 (d, \( J = 8.7 \) Hz, 2H, Ar-H), 7.17-7.22 (m, 1H, Ar-H), 7.41-7.48 (m, 2H, Ar-H), 7.56 (d, \( J = 8.9 \) Hz, 2H, Ar-H); \(^{13}\)C NMR (CDCl\(_3\), 75 MHz): \( \delta = 24.9, 25.1, 28.7, 40.1, 54.6, 57.3, 112.6 120.1, 124.9, 128.1, 138.6, 140.5, 210.4; m/z 313.281 (M\(^+\)).
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XANTHENE

It is well known for many years that dyes have been most widely used in dyeing, as well as high technologies such as lasers, liquid crystalline displays, electro-optical devices and ink-jet printers.¹²

Xanthene derivatives occupy an important position among different families of dyes, owing to a number of reasons related to their photochemical and photophysical properties.³ Xanthene dyes such as fluorescein (1) and its halogenated derivatives eosin (2), erythrosin (3) and rose bengal (4) belongs to the longest known artificial sensitizers of photodynamic effects and diseases caused by light in the presence of molecular oxygen.⁴
In recent years a number of analyte sensors have been designed using these scaffolds via synthesis of new xanthene based dyes. Furthermore, xanthenes and benzoxanthenes have recently received great attention because of their wide range of therapeutic and biological properties. Other useful applications of these heterocycles are like as leucodyes and in laser technologies.

Dean et al. has reported that KBH\textsubscript{4} reduces the carbonyl group of 1'-phenyl-1'H,2H-spiro[naphthalene-1,2'-naphtho[2,1-b]furan]-2-one (6) which is readily obtained by mild oxidation of the 1,1'-(phenylmethylene)dinaphthalen-2-ol (5) followed by the treatment of resulting 1'-phenyl-1'H,2H-spiro[naphthalene-1,2'-naphtho[2,1-b]furan]-2-ol (7) with acid producing the 14-phenyl-14H-dibenzo[a,h]xanthene (8) (Scheme 1).

\[ \text{Scheme 1} \]

The reaction of β-naphthol (9) with 2,5-dimethoxytetrahydrofuran (10) gave the expected 1,2-bis(13-dibenzo[a,j]xanthyl)ethane (11) (Scheme 2).
The alcohols (13) were prepared by treating the appropriate ketone (12) with phenyl magnesium bromine or phenyl lithium in tetrahydrofuran (THF). The corresponding alcohols (13) could be O-alkylated or O-acylated with alkyl halides (14) or alkyl acid chlorides (15) under phase transfer catalyzed conditions in which triethyl-benzylammonium chloride (TEBAC) was used as the phase-transfer agent to yield the antinociceptive active 9-phenyl-oxy or 9-acyl-oxy derivatives (16 & 17) of xanthene and thioxanthene (Scheme 3).11
The reaction of β-naphthol (9) with aromatic aldehydes (18) in acidic media containing AcOH-H$_2$SO$_4$ gave dibenzoxanthenes (19) selectively in quantitative yield without side product formation (Scheme 4).$^{12}$

\[
\begin{align*}
\text{R} = & \text{C}_6\text{H}_5, p-\text{O}_2\text{N}\text{C}_6\text{H}_4, p-\text{H}_3\text{CC}_6\text{H}_4, p-\text{BrC}_6\text{H}_4, p-\text{OHCC}_6\text{H}_4 \\
\end{align*}
\]

Scheme 4

A one-pot condensation of aldehydes (18) with substituted β-naphthols (20) was carried out in the presence of Amberlyst-15 to give 14-substituted-14\textit{H}-dibenzo[\textit{a,j}]xanthenes (21) under solvent-free condition at 125 °C (Scheme 5).$^{13}$

\[
\begin{align*}
\text{R} = & \text{C}_6\text{H}_5, 4-\text{ClC}_6\text{H}_4, 2-\text{ClC}_6\text{H}_4, 4-\text{FC}_6\text{H}_4, 3-\text{FC}_6\text{H}_4, 4-\text{MeC}_6\text{H}_4, 3-\text{F}_3\text{CC}_6\text{H}_4, \text{C}_6\text{H}_5\text{CH}_2, \\
\text{X} = & \text{H, Br} \\
\end{align*}
\]

Scheme 5

A facile synthesis of 14-aryl or alkyl-14\textit{H}-dibenzo[\textit{a,j}]xanthenes (22) was accomplished by treatment of β-naphthol (9) with aryl or alkyl aldehydes (18) under neat conditions in the presence of molecular iodine as a catalyst (Scheme 6).$^{14}$
One-pot three-component condensation reaction of aromatic aldehydes (18), \( \beta \)-naphthol (9) and cyclic 1,3-dicarbonyl compounds (23) was catalyzed by NaHSO\(_4\)-SiO\(_2\) to give the corresponding 12-aryl- or 12-alkyl-8,9,10,12-tetrahydrobenzo[a]xanthen-11-one derivatives (24) in 1,2-dichloromethane (DCM) under reflux conditions \((\text{Scheme 7})^{15}\).

\[
\begin{align*}
(9) + (18) + (23) & \xrightarrow{\text{NaHSO}_4 \cdot \text{SiO}_2, \text{DCM (reflux), 5 h}} (24) \\
\text{R} &= \text{C}_6\text{H}_5, 4-\text{ClC}_6\text{H}_4, 4-\text{O}_2\text{NC}_6\text{H}_4, 3-\text{O}_2\text{NC}_6\text{H}_4, 4-\text{FC}_6\text{H}_4, 4-\text{EtC}_6\text{H}_4, 4-\text{MeC}_6\text{H}_4, 4-\text{HOC}_6\text{H}_4, 4-\text{MeOC}_6\text{H}_4, 3-\text{F}_3\text{C}_6\text{H}_4, 3-\text{MeO}-4-\text{HOC}_6\text{H}_3, \text{CH}_3\text{CH}_2\text{CHO}, (\text{CH}_3)_2\text{CH}
\end{align*}
\]

\textbf{Scheme 7}

The synthesis of 14-aryl-14\( H \)-dibenzo[a,j]xanthenes (26) was achieved through the one-pot condensation of \( \beta \)-naphthol (9) with aryl aldehydes (25) in the presence of sodium lauryl sulphate as phase transfer catalyst in aqueous medium at 100 °C \((\text{Scheme 8})^{16}\).

\[
\begin{align*}
(25) + 2(9) & \xrightarrow{\text{sodium lauryl sulphate, Water, 100 °C}} (26) \\
\text{R} &= \text{H}, 2-\text{Cl}, 3-\text{Cl}, 4-\text{Cl}, 4-\text{NO}_2, 4-\text{CH}_3, 4-\text{CH}_3\text{O}
\end{align*}
\]

\textbf{Scheme 8}
Bazgir et al. described that the reaction of β-naphthol (9) with aromatic aldehydes (18) and dimedone (27) was catalyzed by the Dowex-50W ion exchange resin as reusable eco-friendly catalyst to afford the 14-aryl-14H-dibenzo[a,j]xanthene (22) and 1,8-dioxo-octahydroxanthene derivatives (28) under solvent-free conditions (Scheme 9).17

![Scheme 9](image)

R = C₆H₅, 2-ClC₆H₄, 4-ClC₆H₄, 4-BrC₆H₄, 4-FC₆H₄, 3-O₂NC₆H₄, 4-O₂NC₆H₄, 4-MeC₆H₄

The condensation reaction of substituted aromatic aldehydes (25) with 5,5-dimethyl-1,3-cyclohexanedione (27) was carried out in the presence of a catalytic amount of diammonium hydrogen phosphate as catalyst to give intermediate (29) in water, which was easily converted into corresponding 1,8-dioxo-octahydroxanthene derivatives (30) by the addition of acid in reaction media (Scheme 10).18

![Scheme 10](image)

R = H, 4-Cl, 4-Br, 4-CN, 2,4-Cl₂, 4-OH, 4-MeO, 4-Me, 4-MeCONH, 4-NO₂, 4-CF₃
Ferric hydrogensulfate as a catalyst was used for the one-pot preparation of 14-aryl-14\(H\)-dibenzo[\(a,j\)]xanthene derivatives (26) by cyclocondensation of \(\beta\)-naphthol (9) and substituted benzaldehydes (25) under solvent-free and thermal conditions (Scheme 11).\(^{19}\)

![Scheme 11](attachment:image)

\(R = \text{H, } 4-\text{Cl, } 3-\text{Cl, } 2-4\text{-Cl}_2, 3-\text{NO}_2, 4-\text{NO}_2, 4-\text{OH, } 4-\text{OH-2-MeO, } 4-\text{CH}_3, 2,5-(\text{OCH}_3)_2}\)

A facile, efficient and green synthesis of 14-aryl-14\(H\)-dibenzo[\(a,j\)]xanthenes (22) was developed by one-pot condensation of \(\beta\)-naphthol (9) and aromatic aldehydes (18) in the presence of ytterbium triflates as catalyst in [BPy]BF\(_4\) as ionic liquid at 110 °C (Scheme 12).\(^{20}\)

![Scheme 12](attachment:image)

\(R = \text{C}_6\text{H}_5, 3-\text{ClC}_6\text{H}_4, 4-\text{ClC}_6\text{H}_4, 3-\text{BrC}_6\text{H}_4, 4-\text{BrC}_6\text{H}_4, 3-\text{FC}_6\text{H}_4, 4-\text{FC}_6\text{H}_4, 3-\text{O}_2\text{NC}_6\text{H}_4, 4-\text{O}_2\text{NC}_6\text{H}_4, 4-\text{CNC}_6\text{H}_4, 4-\text{MeC}_6\text{H}_4, 4-\text{MeOC}_6\text{H}_4}\)

One-pot synthesis of aryl-14\(H\)-dibenzo[\(a,j\)]xathene (22) and 1,8-dioxo-octahydroxanthene (28) derivatives was reported by the reaction of \(\beta\)-naphthol (9) or 5,5-dimethyl-1,3-cyclohexanedione (27) with aromatic aldehydes (18) using
montmorillonite K10 as reusable eco-friendly catalyst under solvent-free conditions (Scheme 13).²¹

\[
\begin{align*}
\text{(9)} & \quad \text{OH} \quad \text{R} \quad \text{O} \\
\text{2} & \quad \text{Montmorillonite K10} \\
& \quad \text{Solvent-free} \\
\text{R} = \text{C}_6\text{H}_5, \text{2-ClC}_6\text{H}_4, \text{4-ClC}_6\text{H}_4, \text{4-BrC}_6\text{H}_4, \text{4-FC}_6\text{H}_4, \text{3-O}_2\text{NC}_6\text{H}_4, \text{4-O}_2\text{NC}_6\text{H}_4, \text{4-MeC}_6\text{H}_4
\end{align*}
\]

**Scheme 13**

A convenient procedure for the synthesis of 14-aryl 14\(\text{H}\)-dibenzo[\(a,j\)]xanthenes (22) was reported using the condensation of \(\beta\)-naphthol (9) with aromatic aldehydes (18) in the presence of dipyridine cobalt chloride as the catalyst under solvent-free conditions (Scheme 14).²²

\[
\begin{align*}
\text{(9)} & \quad \text{OH} \quad \text{R} \quad \text{O} \\
\text{2} & \quad \text{CoPy}_2\text{Cl}_2 \\
& \quad 85 \, ^\circ\text{C, Neat conditions} \\
\text{R} = \text{C}_6\text{H}_5, \text{2-ClC}_6\text{H}_4, \text{4-ClC}_6\text{H}_4, \text{4-BrC}_6\text{H}_4, \text{3-BrC}_6\text{H}_4, \text{4-HOC}_6\text{H}_4, \text{2-O}_2\text{NC}_6\text{H}_4, \text{4-O}_2\text{NC}_6\text{H}_4, \\
& \quad \text{4-MeC}_6\text{H}_4, \text{4-MeOC}_6\text{H}_4, \text{2-MeOC}_6\text{H}_4, \text{4-FC}_6\text{H}_4, \text{3-FC}_6\text{H}_4, \text{3-O}_2\text{NC}_6\text{H}_4.
\end{align*}
\]

**Scheme 14**

The condensation reaction involving aromatic aldehydes (25) and 5,5-dimethyl-1,3-cyclohexanedi one (27) was efficiently promoted by the ionic liquid,
[Hbim]BF₄ (IL) as a reaction medium with methanol as co-solvent at ambient temperature under ultrasonic irradiation to afford the corresponding 1,8-dioxo-octahydroxanthene derivatives (31) in excellent yields (Scheme 15).²³

\[
\text{Scheme 15}
\]

Multi-component condensation reaction of β-naphthol (9), aromatic aldehydes (18) and cyclic 1,3-dicarbonyl compounds (23) catalyzed by p-toluenesulfonic acid (p-TSA) was accomplished for the synthesis of a series of 12-aryl-8,9,10,12-tetrahydrobenzo[α]xanthen-11-ones (24) in ionic liquid ([bmim]BF₄) under solvent-free conditions (Scheme 16).²⁴

\[
\text{Scheme 16}
\]

An efficient, general and one-pot procedure for the synthesis of multisubstituted xanthene derivatives (34) through Fe(III)-catalyzed reactions of 2-aryloxybenzaldehydes (32) with substituted indoles (33) was developed in toluene at 50-120 °C (Scheme 17).²⁵
Scheme 17

A simple and expedient method for the synthesis of a series of 14-aryl-14H-dibenzo[<i>a</i>,<i>j</i>]xanthenes (22) as cytotoxic agents was described through a one-pot condensation of β-naphthol (9) with aryl aldehydes (18) catalyzed by TaCl₅ under solvent-free conventional heating (Scheme 18).²⁶

```
R = C₆H₅, 3-MeOC₆H₄, 4-MeC₆H₄, 4-MeOC₆H₄, 2-MeOC₆H₄, 3,4-(MeO)₂C₆H₃, 4-HO-3-MeOC₆H₃, 2-O₂NC₆H₄, 4-O₂NC₆H₄, 3-O₂NC₆H₄
```

Scheme 18

The condensation of β-naphthol (9) with aromatic aldehydes (18) and 2-hydroxynaphthalene-1,4-dione (35) in presence of silica supported perchloric acid was described under solvent-free media to afford the corresponding 14-aryl-14H-dibenzo[<i>a</i>,<i>j</i>]xanthene-8,13-diones (36) in excellent yields and short reaction times (Scheme 19).²⁷
Libraries of benzoxanthenes (24 & 38) were efficiently synthesized via one-pot three component reaction of β-naphthol (9), aldehydes (18) and cyclic 1,3-diketones (23 & 37) in the presence of catalytic amount of ceric ammonium nitrate (CAN) under solvent-free conditions at 120 °C (Scheme 20).28

Surfactant tetradecyltrimethyl ammonium bromide (TTAB) catalyzed convenient and greener synthesis of tetrahydrobenzo[a]xanthene-11-ones (39) was described by the reaction of β-naphthol (9) with aldehydes (18) and dimedone (27) in water (Scheme 21).29
The preparation of 14-aryl(alkyl)-14\(H\)-dibenzo[a,j]xanthene (22) and 1,8-dioxooctahydroxanthene derivatives (28) was introduced by the reaction of aldehydes (18) with \(\beta\)-naphthol (9) and 5,5-dimethyl-1,3-cyclohexanedione (27) in the presence of zirconyl triflate ZrO(OTf)\(_2\) as a reusable catalyst under solvent-free conditions (Scheme 22)\(^{30}\).

12-Molybdophosphoric acid (MPA) encapsulated in the supercages of dealuminated zeolite Y (DAZY) was used as an efficient and reusable catalyst for green synthesis of biologically active 14-substituted aryl-14\(H\)-dibenzo[a,j] xanthene derivatives (26) via three component reaction of \(\beta\)-naphthol (9) with substituted
aromatic aldehydes (25) under conventional heating and microwave irradiation conditions (Scheme 23).  

\[
\begin{align*}
\text{R} &= \text{2-Cl, 4-Cl, 2,4-Cl}_2, 2-\text{OH, 2-OH-5-NO}_2, 3-\text{NO}_2, 4-\text{NO}_2, 4-\text{CH}_3, 2-\text{OCH}_3, 3-\text{OCH}_3, \\
&\quad 4-\text{OCH}_3, 2,3-(\text{OCH}_3)_2, 3,4-(\text{OCH}_3)_2
\end{align*}
\]

Scheme 23

A multicomponent condensation of β-naphthol (9), aromatic aldehydes (25) and 1,3-cyclocarbonyl compounds was described (27 & 40) in the presence of chlorosulphonic acid (ClSO$_3$H) as a catalyst to furnish 12-aryl-8,9,10,12-tetrahydrobenzo[a]xanthen-11-one derivatives (41 & 42) in good to excellent yields under ultrasound and solvent-free conditions at room temperature (Scheme 24).  

\[
\begin{align*}
\text{R} &= \text{H, 2-Cl, 4-Cl, 2-OH, 4-OH, 4-OH-3-OCH}_3, 2-\text{NO}_2, \\
&\quad 4-\text{NO}_2, 2-\text{OCH}_3, 4-\text{OCH}_3,
\end{align*}
\]

Scheme 24
OBJECT OF THE PRESENT WORK

The development of highly efficient and sustainable procedures has become a major driving force to assemble the biologically active compounds in the field of academia and industry. Multicomponent reaction (MCR) is a process in which three or more components are combined together in a single reaction vessel to produce a final product. The versatility and effectiveness as potential multicomponent substrate have been used in various MCRs such as Hantzsch reaction, Biginelli reaction, Schopf's tropinone synthesis, Tietze’s reaction, Ugi and Mannich type reactions.

Nevertheless, the development of MCRs is still in demand. In this context, ortho-quinone methides (O-QMs) intermediate has been utilized in many tandem processes and [4+2] cycloaddition with a wide range of dienophiles. However, with carbon nucleophiles only limited works have been reported. It is difficult to creat the reaction conditions for proper exploitation of O-QMs in reactions with carbon nucleophiles for organic synthesis.

Xanthene and its derivatives are known as important class of heterocyclic compounds, widely used as lecodyes, P-sensitive fluorescent materials for visualization of biomolecules and are utilized in laser technologies due to their photochemical and photophysical properties. They possess diverse biological and therapeutic properties such as anti-inflammatory, antiviral and antibacterial activities. These compounds are being utilized as antagonists for paralyzing action of zoxazolamine and in photodynamic therapy. Among the molecules of this class, benzoaxanthen is a prominent structural motif found in various natural products and synthetic compounds with important biological activities.
Although, several methods have been reported for the synthesis of tetrahydrobenzo[a]-xanthen-11-one and benzo[f]chromen-3-one derivatives\(^{53}\), these procedures have limitations of long reaction time, harsh reaction conditions and often required expensive catalysts. As a consequence, the development of mild and practical procedure for accessing these benzoaxanthen derivatives remains an elusive goal. Recently, lanthanide compounds have become attractive candidates for use as Lewis acid catalysts in organic chemistry with numerous applications as promoters.\(^{54}\) The introduction of electronegative ligands such as chloride enhances the activity by increasing the Lewis acidity of the metal.\(^{55}\) These catalysts offer several advantages including mild reaction conditions, clean reactions, shorter reaction times, lower catalyst loading and simple experimental procedures with high yield.

In this context, cerium(III) chloride has received as an inexpensive, non-toxic, water tolerant and potentially useful Lewis acid catalyst\(^{56}\) for several organic reactions.\(^{57}\) The activity of cerium(III) chloride was increased in combination with NaI.\(^{58}\) As a part of our ongoing program on the development of new synthetic methods\(^ {59}\) and to examine the behaviour of cerium(III) chloride as catalyst\(^ {60}\) in the synthesis of organic compounds.\(^ {61}\) Herein, we wish to report a mild and efficient protocol for the synthesis of tetrahydrobenzo[a]-xanthen-11-one derivatives (47a-j & 48a-c) via one-pot three-component reaction of aromatic aldehydes (43), β-naphthol (44) and 1,3-dicarbonyl compounds (45 & 46) using cerium(III) chloride as catalyst in methanol at 50 °C (Scheme 25).
RESULTS AND DISCUSSION

To find the optimum reaction conditions, a mixture of β-naphthol (1 mmol), benzaldehyde (1 mmol) and 5,5-dimethyl-1,3-cyclohexanedione (1.2 mmol) in methanol (5 mL) were stirred at 50 °C under various reaction conditions (Table 1). Reaction was completed within 8 h in the absence of catalyst. However, under the same reaction conditions by employing 1 mol% of CeCl₃.7H₂O, the reaction afforded expected product up to 25% yield within 5 h of reaction time (Table 1, Entry 2).

With this optimistic result in hand, we further investigated the best reaction conditions by using different amount of CeCl₃.7H₂O. An increase in the quantity of CeCl₃.7H₂O from 1 mol% to 3 mol% not only decreases the reaction time from 5 h to 2 h but also increased the product yield slightly from 25% to 90% (Table 1, Entry 4). In a search for an even higher yield, we decided to employ NaI as an additive with CeCl₃.7H₂O (CeCl₃.7H₂O-NaI system). In this context, the effect of the amounts of the NaI and CeCl₃.7H₂O was evaluated. When the reaction was carried out by using CeCl₃.7H₂O-NaI (3 mol%) in methanol (5 mL), the product yield was nearly same (Table 2, Entry 3) as the yield obtained with CeCl₃.7H₂O (3 mol%) (Table 2, Entry 2). The rate of this reaction was slightly improved by adding 5 mol% of CeCl₃.7H₂O-NaI, and the desired product was obtained in 2 h. Thus we found that 3 mol% CeCl₃.7H₂O is better suited than the CeCl₃.7H₂O-NaI system for the optimum yield of tetrahydrobenzo[a]-xanthen-11-one derivatives (Table 2).

Further, we have also scrutinized this reaction by using various Lewis acid catalysts such as CuSO₄, CeCl₃.7H₂O, Y(OTf)₃, AlCl₃, ZnCl₂ and Sr(OTf)₂. Comparative studies show that CeCl₃.7H₂O is more effective catalyst for this condensation reaction (Table 2, Entry 2).
It is well known that the reaction medium plays an important role in the catalytic reaction. To study the influence of the nature of solvent for this reaction using CeCl₃·7H₂O as a catalyst was carried out at a temperature (50 °C) in different solvents, such as acetonitrile, THF, toluene, methanol and dichloromethane (Table 3). The highest reaction activity was achieved in the system using methanol as a solvent in comparison to other solvents under similar reaction conditions (Table 3, Entry 4). The results show that the catalytic performance is strongly affected by the type of solvent but a direct correlation between solvent properties and their efficiency could not be established in any case.

Encouraged by these remarkable results, we screened a variety of aromatic and heterocyclic aldehydes with β-naphthol and 5,5-dimethyl-1,3-cyclohexanedione to obtain the corresponding products. The results are summarized in Table 4. In all cases, various aromatic aldehydes with electron-donating and electron-withdrawing substituents were reacted successfully giving the products in good to excellent yields. It was observed that substituents in the aromatic ring of aldehydes have a delicate effect on the reaction process. Aromatic aldehydes with electron-withdrawing groups reacted faster than those with electron-donating groups. In order to broaden the scope of the present method, the replacement of 5,5-dimethyl-1,3-cyclohexanedione with 1,3-cyclohexanedione was also examined. Under the similar conditions, the reactions proceeded steadily to afford a series of 12-phenyl-8,9,10,12-tetrahydrobenzo[a]-xanthen-11-one derivatives with good yields (Table 4, Entries 11-13).

A tentative mechanism for the formation of tetrahydrobenzo[a]-xanthen-11-ones (47a-j) is proposed in Scheme 26. By following the literatures, we suppose that the reaction might have proceeded via ortho-quinone methides intermediate (I) which was formed by the nucleophilic addition of β-naphthol (44) to aldehydes (43)
catalyzed by CeCl$_3$. Subsequent substitution of the oxygen atom, coordinated by CeCl$_3$ with 5,5-dimethyl-1,3-cyclohexanedione (45) afforded (III) and (IV) through the formation of intermediate (II). The compound (IV) eliminated one molecule of H$_2$O and afforded desired product (47a-j).

Further to realize the generality and versatility of the catalyst, this novel protocol was extended for the condensation of aromatic aldehydes (43), β-naphthol (44) and Meldrum’s acid (49). During the experiments, it was observed that different aromatic aldehydes bearing electron-withdrawing groups underwent smoothly in the presence of 3 mol% of CeCl$_3$.7H$_2$O at 50 °C in methanol to afford the high yield of benzo[f]chromen-3-ones (50a-e) (Scheme 27, Table 5, Entries 2 and 3).

Mechanistically, to clarify the scheme 28 for the synthesis of benzo[f]chromen-3-one derivatives, a mechanism was proposed. The reaction may be rationalized by the condensation of β-naphthol (44) with aldehydes (43) catalyzed by CeCl$_3$ and the initial formation of ortho-quinone methides intermediate (I) takes place which may be attacked by enol tautomer of Meldrum’s acid (49) leading to the intermediate (V) through the formation of intermediate (II). The intermediate (V) may undergo the formation of benzo[f]chromen-3-one derivatives as product (50a-e) followed by the removal of acetone and carbon dioxide molecules (Scheme 28).
Scheme 25: CeCl$_3$.7H$_2$O catalyzed condensation of β-naphthol, aldehydes and cyclic 1,3-dicarbonyl compounds.

Scheme 26: Proposed mechanism for the condensation reaction of aldehydes, β-naphthol and 5,5-dimethyl-1,3-cyclohexanedione.
Scheme 27: Synthesis of benzo[f]chromen-3-one derivatives using Meldrum’s acid.

\[
\text{R} = \text{C}_6\text{H}_5, \text{4-ClC}_6\text{H}_4, \text{4-FC}_6\text{H}_4, \text{4-CH}_3\text{OC}_6\text{H}_4, \text{2-Thienyl}
\]

Scheme 28: Proposed mechanism for the condensation reaction of aldehydes, β-naphthol and Meldrum’s acid.
EXPERIMENTAL

Aldehydes (1.0 mmol), β-naphthol (1.0 mmol) and 5 mL of methanol were placed in a 50 mL round bottom flask over a magnetic stirrer. Cerium(III) chloride (3 mol%)/(0.03 mmol, 11.12 mg) was added to the mixture and the contents were stirred at 50 °C for an appropriate time. To this stirred mixture, cyclic 1,3-dicarbonyl compounds/Meldrum’s acid (1.2 mmol) were added. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was allowed to cool at room temperature and water was added to the reaction mixture and then extracted with ethyl acetate (3 × 10 mL). The organic layer was dried over anhydrous Na₂SO₄ and evaporated. The crude product was purified by column chromatography (hexane/ethyl acetate, 80:20) to provide the pure products. All the products were synthesized by novel route and elucidated comparing with authentic literature.⁵³,⁶²,⁶⁴
Table 1: Optimization of the concentration of CeCl₃.7H₂O for the synthesis of tetrahydrobenzo[a]-xanthen-11-ones.a

<table>
<thead>
<tr>
<th>Entry</th>
<th>CeCl₃.7H₂O (mol%)</th>
<th>Time (h)</th>
<th>Yield (%)ᵇ</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>5</td>
<td>25</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>2</td>
<td>60</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>2</td>
<td>90</td>
</tr>
</tbody>
</table>

*aReaction conditions: benzaldehyde (1.0 mmol), β-naphthol (1.0 mmol), 5,5-dimethyl-1,3-cyclohexanediene (1.2 mmol), catalyst CeCl₃.7H₂O; solvent CH₃OH (5 mL); temperature 50 ºC.
bIsolated yields.

Table 2: Evaluation of catalytic activity of various catalysts for the synthesis of tetrahydrobenzo[a]-xanthen-11-ones.a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Mol%</th>
<th>Time (h)</th>
<th>Yield (%)ᵇ</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CuSO₄</td>
<td>10</td>
<td>8</td>
<td>25</td>
</tr>
<tr>
<td>2</td>
<td>CeCl₃.7H₂O</td>
<td>3</td>
<td>2</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>CeCl₃.7H₂O-NaI</td>
<td>3</td>
<td>2</td>
<td>91</td>
</tr>
<tr>
<td>4</td>
<td>CeCl₃.7H₂O-NaI</td>
<td>5</td>
<td>2</td>
<td>93</td>
</tr>
<tr>
<td>5</td>
<td>Y(OTf)₃</td>
<td>10</td>
<td>5</td>
<td>35</td>
</tr>
<tr>
<td>6</td>
<td>AlCl₃</td>
<td>10</td>
<td>5</td>
<td>45</td>
</tr>
<tr>
<td>7</td>
<td>ZnCl₂</td>
<td>10</td>
<td>5</td>
<td>30</td>
</tr>
<tr>
<td>8</td>
<td>Sr(OTf)₂</td>
<td>10</td>
<td>5</td>
<td>85</td>
</tr>
</tbody>
</table>

*aReaction conditions: benzaldehyde (1.0 mmol), β-naphthol (1.0 mmol), 5,5-dimethyl-1,3-cyclohexanediene (1.2 mmol), different catalysts; solvent CH₃OH (5 mL); temperature 50 ºC.
bIsolated yields.

Table 3: Effect of Solvent.a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Yield (%)ᵇ</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Acetonitrile</td>
<td>42</td>
</tr>
<tr>
<td>2</td>
<td>THF</td>
<td>25</td>
</tr>
<tr>
<td>3</td>
<td>Toluene</td>
<td>12</td>
</tr>
<tr>
<td>4</td>
<td>Methanol</td>
<td>90</td>
</tr>
<tr>
<td>5</td>
<td>Dichloromethane</td>
<td>30</td>
</tr>
</tbody>
</table>

*aReaction conditions: benzaldehyde (1.0 mmol), β-naphthol (1.0 mmol), 5,5-dimethyl-1,3-cyclohexanediene (1.2 mmol) catalyst CeCl₃.7H₂O (3 mol%); different solvent (5 mL); time (2 h); temperature 50 ºC.
bIsolated yields.
### Table 4: Synthesis of tetrahydrobenzo[α]-xanthen-11-one derivatives using CeCl₃·7H₂O.ᵃ

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehydes (R)</th>
<th>1,3-dicarbonyl compounds</th>
<th>Product</th>
<th>Time (h)</th>
<th>Yield (%)ᵇ</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>C₆H₅</td>
<td>3</td>
<td>47a</td>
<td>2</td>
<td>90</td>
</tr>
<tr>
<td>2</td>
<td>4-ClC₆H₄</td>
<td>3</td>
<td>47b</td>
<td>2.5</td>
<td>95</td>
</tr>
<tr>
<td>3</td>
<td>4-BrC₆H₄</td>
<td>3</td>
<td>47c</td>
<td>2.5</td>
<td>95</td>
</tr>
<tr>
<td>4</td>
<td>4-H₃CC₆H₄</td>
<td>3</td>
<td>47d</td>
<td>3</td>
<td>89</td>
</tr>
<tr>
<td>5</td>
<td>4-CH₃OC₆H₄</td>
<td>3</td>
<td>47e</td>
<td>3.5</td>
<td>87</td>
</tr>
<tr>
<td>6</td>
<td>4-O₂NC₆H₄</td>
<td>3</td>
<td>47f</td>
<td>2</td>
<td>90</td>
</tr>
<tr>
<td>7</td>
<td>4-HOC₆H₄</td>
<td>3</td>
<td>47g</td>
<td>2.5</td>
<td>83</td>
</tr>
<tr>
<td>8</td>
<td>2-Naphthyl</td>
<td>3</td>
<td>47h</td>
<td>2</td>
<td>89</td>
</tr>
<tr>
<td>9</td>
<td>Piperonyl</td>
<td>3</td>
<td>47i</td>
<td>2</td>
<td>76</td>
</tr>
<tr>
<td>10</td>
<td>2-Thienyl</td>
<td>3</td>
<td>47j</td>
<td>2</td>
<td>78</td>
</tr>
<tr>
<td>11</td>
<td>C₆H₅</td>
<td>4</td>
<td>48a</td>
<td>3</td>
<td>87</td>
</tr>
<tr>
<td>12</td>
<td>4-ClC₆H₄</td>
<td>4</td>
<td>48b</td>
<td>2.5</td>
<td>94</td>
</tr>
<tr>
<td>13</td>
<td>4-O₂NC₆H₄</td>
<td>4</td>
<td>48c</td>
<td>2</td>
<td>91</td>
</tr>
</tbody>
</table>

ᵃReaction conditions: aldehydes (1.0 mmol), β-naphthol (1.0 mmol), 1,3-dicarbonyl compounds (1.2 mmol), catalyst CeCl₃·7H₂O (3 mol%); solvent CH₃OH (5 mL); temperature 50 ºC.
ᵇIsolated yields.

### Table 5: Synthesis of benzo[f]chromen-3-one derivatives catalyzed by CeCl₃·7H₂O.ᵃ

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Product</th>
<th>Time (h)</th>
<th>Yield (%)ᵇ</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>C₆H₅</td>
<td>50a</td>
<td>3.5</td>
<td>89</td>
</tr>
<tr>
<td>2</td>
<td>4-ClC₆H₄</td>
<td>50b</td>
<td>2</td>
<td>92</td>
</tr>
<tr>
<td>3</td>
<td>4-FC₆H₄</td>
<td>50c</td>
<td>2.5</td>
<td>94</td>
</tr>
<tr>
<td>4</td>
<td>4-CH₃OC₆H₄</td>
<td>50d</td>
<td>6</td>
<td>70</td>
</tr>
<tr>
<td>5</td>
<td>2-Thienyl</td>
<td>50e</td>
<td>3</td>
<td>80</td>
</tr>
</tbody>
</table>

ᵃReaction conditions: aldehydes (1.0 mmol), β-naphthol (1.0mmol), Meldrum’s Acid (1.2 mmol), catalyst CeCl₃·7H₂O (3 mol%); solvent CH₃OH (5 mL); temperature 50 ºC.
ᵇIsolated yields.
Spectroscopic data of synthesized tetrahydrobenzo[a]-xanthen-11-one (47a-j & 48a-c) and benzo[f]chromen-3-one derivatives (50a-e)

9,9-Dimethyl-12-phenyl-8,9,10,12-tetrahydrobenzo[a]-xanthen-11-one (47a): White solid; m.p. 152–153 °C; IR (KBr/cm−1): \( \nu_{\text{max}} = 3059, 2960, 2874, 1632, 1379, 1223, 1169, 1075, 812; \) \(^1\)H NMR (CDCl₃, 400 MHz): \( \delta = 7.98 (d, J = 8.0 \text{ Hz}, 1H), 7.70-7.76 (m, 2H), 7.40-7.42 (m, 1H), 7.29-7.38 (m, 4H), 7.14 (t, J = 7.5 \text{ Hz}, 1H), 7.08 (t, J = 7.4 \text{ Hz}, 2H), 4.77 (s, 1H), 2.45 (s, 2H), 2.27 (d, J =17.1 Hz, 1H), 2.21 (d, J =17.1 Hz, 1H), 1.10 (s, 3H), 0.97 (s, 3H); \(^{13}\)C NMR (CDCl₃, 100 MHz): \( \delta = 196.1, 165.2, 147.9, 144.8, 130.5, 130.7, 129.1, 128.6, 128.5, 128.3, 127.1, 126.4, 124.7, 123.8, 116.7, 116.1, 113.3, 51.1, 40.6, 34.9, 32.4, 29.5, 27.4; m/z 355.1653 (M+1, C₂₅H₂₂O₂ requires 354.1620).

12-(4-Chlorophenyl)-9,9-dimethyl-8,9,10,12-tetrahydrobenzo[a]-xanthen-11-one (47b): White solid; m.p. 183–184 °C; IR (KBr/cm−1): \( \nu_{\text{max}} = 3056, 2960, 1602, 1513, 1381, 1217, 1168, 1019, 960, 847, 748; \) \(^1\)H NMR (CDCl₃, 400 MHz): \( \delta = 7.97 (d, J = 8.4 \text{ Hz}, 1H), 7.77 (d, J = 6.1 \text{ Hz}, 1H), 7.75 (d, J = 8.4 \text{ Hz}, 1H), 7.39-7.43 (m, 1H), 7.30-7.33 (m, 1H), 7.29 (d, J = 8.7 \text{ Hz}, 1H), 7.27 (s, 2H), 7.14 (d, J = 8.2 \text{ Hz}, 2H), 4.73 (s, 1H) 2.55 (s, 2H), 2.56 (s, 2H), 2.45 (d, J =16.1 Hz, 1H), 2.27(d, J =16.1 Hz, 1H), 1.08 (s, 3H), 0.98 (s, 3H); \(^{13}\)C NMR (CDCl₃, 100 MHz): \( \delta = 196.4, 164.2, 147.4, 143.5, 131.7, 131.4, 130.1, 129.3, 128.7, 128.8, 127.2, 125.3, 123.7, 117.2, 114.1, 51.6, 41.2, 34.4, 32.5, 29.2, 27.3; m/z 390.1201 (M+1, C₂₅H₂₁ClO₂ requires 388.1230).

12-(4-Bromophenyl)-9,9-dimethyl-8,9,10,12-tetrahydrobenzo[a]-xanthen-11-one (47c): White solid; m.p. 184–186 °C; IR (KBr/cm−1): \( \nu_{\text{max}} = 3059, 2961, 1643, 1591, 1482, 1401, 1373, 1221, 1173, 1144, 1006, 960, 845, 745; \) \(^1\)H NMR (CDCl₃, 400
Chapter IV B

9,9-Dimethyl-12-p-tolyl-8,9,10,12-tetrahydrobenzo[a]-xanthen-11-one (47d):
White solid; m.p. 178–179 °C; IR (KBr/cm⁻¹): νmax = 3044, 2959, 2865, 1610, 1513, 1383, 1219, 1019, 846; ¹H NMR (CDCl₃, 400 MHz): δ = 7.99 (d, J = 8.4 Hz, 1H), 7.65-7.79 (m, 2H), 7.39-7.41 (m, 1H), 7.30-7.33 (m, 2H), 7.14-7.25 (m, 2H), 7.02 (d, J = 8.0 Hz, 2H), 4.73 (s, 1H), 2.56 (s, 2H), 2.45 (d, J = 16.3 Hz, 1H), 2.22 (d, J = 16.3 Hz, 1H), 2.15 (s, 3H), 1.09 (s, 3H), 0.98 (s, 3H); ¹³C NMR (CDCl₃, 100 MHz): δ = 196.1, 163.2, 153.2, 146.4, 140.6, 134.7, 133.7, 130.4, 128.5, 127.8, 127.1, 126.5, 125.8, 123.9, 122.5, 117.1, 116.5, 115.8, 113.1, 49.6, 40.2, 33.1, 31.1, 28.3, 26.1, 19.4; m/z 369.1810 (M+1, C₂₆H₂₄O₂ requires 368.1776).

12-(4-Methoxyphenyl)-9,9-dimethyl-8,9,10,12-tetrahydrobenzo[a]-xanthen-11-one (47e): White solid; m.p. 206–208 °C; IR (KBr/cm⁻¹): νmax = 3018, 2963, 2843, 1677, 12.18, 1161, 1028, 960, 847, 756; ¹H NMR (CDCl₃, 400 MHz): δ = 7.85 (d, J = 8.4 Hz, 1H), 7.74 (t, J = 9.3 Hz, 2H), 7.41 (t, J = 7.3 Hz, 1H), 7.39 (t, J = 7.2 Hz, 1H), 7.30 (d, J = 8.9 Hz, 1H), 7.25 (d, J = 8.7 Hz, 2H), 6.69 (d, J = 8.6 Hz, 2H), 5.40 (s, 1H), 3.68 (s, 3H), 2.45 (s, 2H), 2.27 (d, J = 16.2 Hz, 1H), 2.21 (d, J = 16.2 Hz, 1H), 1.07 (s, 3H), 0.96 (s, 3H); ¹³C NMR (CDCl₃, 100 MHz): δ = 197.1, 163.8, 157.9, 147.8, 137.3, 131.6, 129.5, 128.8, 128.5, 127.1, 125.1, 123.9, 118.1, 117.3, 114.7,
113.7, 55.2, 51.3, 41.5, 33.9, 32.4, 29.4, 27.3; m/z 385.1759 (M+1, C_{26}H_{24}O_{3} requires 384.1725).

9,9-Dimethyl-12-(4-nitrophenyl)-8,9,10,12-tetrahydrobenzo-[a]-xanthen-11-one (47f): White solid; m.p. 174–176 °C; IR (KBr/cm⁻¹): ν_{max} = 3075, 2960, 1668, 1652, 1596, 1519, 1347, 1313, 1224, 1165, 960, 832, 756; ¹H NMR (CDCl₃, 400 MHz): δ = 8.04 (d, J = 8.8 Hz, 2H), 7.79-7.84 (m, 3H), 7.34-7.53 (m, 5H), 4.82 (s, 1H), 2.59 (s, 2H), 2.36 (d, J = 16.5 Hz, 1H), 2.22 (d, J = 16.5 Hz, 1H), 1.11 (s, 3H), 0.98 (s, 3H);
¹³C NMR (CDCl₃, 100 MHz): δ = 196.5, 165.2, 147.6, 143.9, 132.1, 131.8, 131.5, 130.0, 129.3, 128.7, 128.6, 127.3, 125.2, 123.7, 117.1, 117.2, 114.1, 51.2, 41.6, 34.4, 32.5, 29.5, 27.3; m/z 400.1504 (M+1, C_{25}H_{21}NO_{4} requires 399.1471).

12-(4-Hydroxyphenyl)-9,9-dimethyl-8,9,10,12-tetrahydrobenzo[a]-xanthen-11-one (47g): White solid; m.p. 152–153 °C; IR (KBr/cm⁻¹): ν_{max} = 3312, 2956, 1636, 1599, 1381, 1216, 1160, 959, 841, 742; ¹H NMR (CDCl₃, 400 MHz): δ = 7.77 (d, J = 8.3 Hz, 1H), 7.64-7.66 (m, 2H), 7.42 (t, J = 8.0 Hz, 1H), 7.32 (t, J = 7.4 Hz, 1H), 7.28 (d, J = 8.8 Hz, 1H), 7.14 (d, J = 8.4 Hz, 2H), 6.89 (s, 1H), 6.62 (d, J = 8.4 Hz, 2H), 5.01 (s, 1H), 4.69 (s, 1H), 2.45 (s, 1H), 2.26 (d, J = 16.4 Hz, 1H), 2.22 (d, J = 16.4 Hz, 1H), 1.08 (s, 3H), 0.96 (s, 3H); ¹³C NMR (CDCl₃, 100 MHz): δ = 198.4, 164.4, 154.2, 147.8, 136.2, 131.6, 131.5, 129.4, 128.9, 128.8, 126.1, 125.2, 123.9, 118.9, 117.2, 115.6, 114.3, 51.2, 41.3, 33.4, 32.6, 29.4, 27.3; m/z 371.1602 (M+1, C_{25}H_{22}O_{3} requires 370.1569).

9,9-Dimethyl-12-(naphthalen-2-yl)-8,9,10,12-tetrahydrobenzo[a]-xanthen-11-one (47h): White solid; m.p. 234–235 °C; IR (KBr/cm⁻¹): ν_{max} = 3057, 2959, 1693, 1513, 1380, 1218, 1168, 960; ¹H NMR (CDCl₃, 400 MHz): δ = 8.03 (d, J = 8.3 Hz, 1H), 7.62 (s, 1H), 7.70-7.81 (m, 3H), 7.57 (d, J = 7.7 Hz, 1H), 7.63 (d, J = 8.8 Hz, 1H), 7.42 (d, J = 8.3 Hz, 1H), 7.31-7.40 (m, 5H), 5.78 (s, 1 H), 2.54 (s, 2H), 2.26 (q, J =
16.1 Hz, 2H), 1.12 (s, 3H), 0.94 (s, 3H); $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta = 198.2, 163.2, 147.1, 141.3, 133.5, 132.3, 131.7, 131.6, 129.1, 128.6, 128.3, 128.2, 127.6, 127.4, 127.3, 126.9, 125.9, 125.7, 125.1, 123.9, 117.8, 117.3, 114.23, 51.2, 40.6, 34.1, 32.4, 29.5, 27.4; m/z 405.1810 (M+1, C$_{29}$H$_{24}$O$_2$ requires 404.1776).

12-{{Benzo[d][1,3]dioxol-5-yl}}-9,9-dimethyl-8,9,10,12-tetrahydrobenzo[a]-xanthen-11-one (47i): White solid; m.p. 214–215 °C; IR (KBr/cm$^{-1}$): $\nu_{\text{max}}$ = 3210, 2960, 1667, 1503, 1361, 1230, 1138, 1039, 960, 847, 748, 621; $^1$H NMR (CDCl$_3$, 400 MHz): $\delta = 7.98$ (d, $J$ = 8.4 Hz, 1H), 7.79 (d, $J$ = 8.5 Hz, 1H), 7.72 (d, $J$ = 9.0 Hz, 1H), 7.40 (td, $J$ = 7.0, 1.2 Hz, 1H), 7.39 (td, $J$ = 7.9, 0.9 Hz, 1H), 7.34 (d, $J$ = 8.9 Hz, 1H), 6.86 (dd, $J$ = 8.0, 1.7 Hz, 1H), 6.77 (d, $J$ = 1.6 Hz, 1H), 6.62 (d, $J$ = 8.0 Hz, 1H), 5.80 (s, 2H), 4.72 (s, 1H), 2.42 (s, 2H), 2.31 (d, $J$ = 16.4 Hz, 1H), 2.23 (d, $J$ = 16.4 Hz, 1H), 1.06 (s, 3H), 0.98 (s, 3H); $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta = 197.5$, 164.1, 147.9, 147.7, 146.3, 138.2, 131.7, 131.6, 129.3, 128.6, 127.5, 125.4, 123.9, 121.9, 117.9, 117.3, 114.5, 109.2, 108.3, 101.5, 51.2, 41.6, 34.5, 32.6; m/z 399.1552 (M+1, C$_{26}$H$_{22}$O$_4$ requires 398.1518).

9,9-Dimethyl-12-(thiophen-2-yl)-8,9,10,12-tetrahydrobenzo[a]-xanthen-11-one (47j): White solid; m.p. 183-184 °C; IR (KBr/cm$^{-1}$): $\nu_{\text{max}}$ = 3124, 2926, 1629, 1513, 1388, 1215, 1171, 1148, 1010, 811, 746; $^1$H NMR (CDCl$_3$, 400 MHz): $\delta = 7.78$-7.73 (m, 2H), 7.68 (d, $J$ = 8.5 Hz, 1H), 7.29-7.43 (m, 3H), 7.20-7.25 (m, 1H), 7.09-7.16 (m, 2H), 5.57 (s, 1H), 3.68 (s, 2H), 2.45 (s, 2H), 1.25 (s, 3H), 1.07 (s, 3H); $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta = 196.7$, 164.5, 148.4, 147.9, 131.5, 129.2, 128.3, 127.1, 126.2, 125.2, 125.1, 124.2, 123.3, 117.3, 117.2, 113.7, 50.8, 41.2, 32.1, 29.3, 29.2, 27.1; m/z 361.1218 (M+1, C$_{23}$H$_{20}$O$_2$S requires 360.1186).

12-Phenyl-8,9,10,12-tetrahydrobenzo[a]-xanthen-11-one (48a): White solid; m.p. 191-192 °C; IR (KBr/cm$^{-1}$): $\nu_{\text{max}}$ = 3131, 3053, 2956, 1647, 1593, 1453, 1372, 1228,
1190, 998, 956, 817, 759, 702, 532; \(^1^H\) NMR (CDCl\(_3\), 400 MHz): \(\delta = 7.95\) (d, \(J = 8.5\) Hz, 1H), 7.76-7.77 (m, 2H), 7.30-7.45 (m, 5H), 7.14-7.17 (m, 2H), 7.03-7.09 (m, 1H), 4.72 (s, 1H), 2.65-2.76 (m, 2H), 2.33-2.48 (m, 2H), 1.95-2.07 (m, 2H); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \(\delta = 197.2, 165.4, 147.9, 145.2, 131.4, 131.5, 128.8, 128.4, 128.5, 128.3, 127.1, 126.2, 124.8, 123.6, 117.8, 117.1, 115.5, 37.2, 34.6, 27.7, 20.2; m/z 327.1340 (M+1, C\(_{23}\)H\(_{18}\)O\(_2\) requires 326.1307).

12-(4-Chlorophenyl)-8,9,10,12-tetrahydrobenzo[\(a\)]-xanthen-11-one (48b): White solid; m.p. 208-209 °C; IR (KBr/cm\(^{-1}\)): \(\nu_{\text{max}} = 3132, 3051, 2960, 1648, 1592, 1487, 1367, 1229, 1190, 1141, 1088, 1008, 955, 817, 754, 531\); \(^1^H\) NMR (CDCl\(_3\), 400 MHz): \(\delta = 7.89\) (d, \(J = 8.5\) Hz, 1H), 7.77-7.78 (m, 2H), 7.24-7.43 (m, 5H), 7.13-7.15 (m, 2H), 4.71 (s, 1H), 2.62-2.75 (m, 2H), 2.34-2.47 (m, 2H), 1.92-2.07 (m, 2H); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \(\delta = 197.2, 165.7, 147.5, 143.7, 132.1, 131.2, 129.6, 129.3, 128.4, 127.4, 125.6, 123.3, 117.2, 117.1, 115.2, 37.3, 34.3, 27.7, 20.2; m/z 362.0888 (M+1, C\(_{23}\)H\(_{17}\)ClO\(_2\) requires 360.0917).

12-(4-Nitrophenyl)-8,9,10,12-tetrahydrobenzo[\(a\)]-xanthen-11-one (48c): White solid; m.p. 237–238 °C; IR (KBr/cm\(^{-1}\)): \(\nu_{\text{max}} = 3076, 2932, 1644, 1596, 1515, 1342, 1224, 1176, 1025, 961, 847, 752\); \(^1^H\) NMR (CDCl\(_3\), 400 MHz): \(\delta = 8.04\) (d, \(J = 8.4\) Hz, 2H), 7.79-7.83 (m, 3H), 7.52 (d, \(J = 8.9\) Hz, 2H), 7.35-7.46 (m, 3H), 4.75 (s, 1H), 2.71-2.80 (m, 2H), 2.37-2.49 (m, 2H), 2.06-2.12 (m, 1H), 1.95-2.01 (m, 1H); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \(\delta = 197.5, 166.3, 152.4, 147.8, 146.3, 131.6, 131.3, 129.9, 129.6, 128.4, 127.6, 125.5, 123.7, 123.3, 117.2, 116.3, 114.4, 37.1, 35.1, 27.9, 20.4; m/z 372.1191 (M+1, C\(_{23}\)H\(_{17}\)NO\(_4\) requires 371.1158).

1-Phenyl-1\(\text{H}\)-benzo[\(f\)]chromen-3(2\(\text{H}\))-one (50a): White solid; m.p. 117-119 °C; IR (KBr/cm\(^{-1}\)): \(\nu_{\text{max}} = 3058, 2983, 1735, 1629, 1454, 1212, 1029, 960\); \(^1^H\) NMR (CDCl\(_3\), 400 MHz): \(\delta = 7.87\) (d, \(J = 8.5\) Hz, 2H), 7.67 (d, \(J = 8.0\) Hz, 1H), 7.39-7.45 (m, 2H),
7.31 (d, $J = 6.8$ Hz, 1H), 7.24-7.30 (m, 3H), 7.15 (d, $J = 7.5$ Hz, 2H), 4.92 (dd, $J = 7.3$, 3.4 Hz, 1H), 3.35-3.40 (m, 2H); $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta = 169.3, 150.1, 140.4, 132.8, 131.2, 130.6, 129.6, 127.9, 127.7, 127.5, 126.9, 124.3, 123.5, 116.7, 116.4, 37.2, 36.8; m/z 275.1027 (M+1, C$_{19}$H$_{14}$O$_2$ requires 274.0994).

1-(4-Chlorophenyl)-1$H$-benzo[f]chromen-3(2$H$)-one (50b): Colourless oil; IR (Film/cm$^{-1}$): $\nu_{\text{max}} = 3058, 2955, 1738, 1630, 1436, 1213, 1173, 1092, 960, 847, 749; ^1H NMR (CDCl$_3$, 400 MHz): $\delta = 7.70$-7.98 (m, 2H), 7.67 (d, $J = 8.2$ Hz, 1H), 7.39-7.43 (m, 2H), 7.32 (d, $J = 8.6$ Hz, 1H), 7.22 (d, $J = 8.3$ Hz, 2H), 7.10 (d, $J = 7.8$ Hz, 2H), 4.91 (d, $J = 5.8$ Hz, 1H), 3.76 (dd, $J = 10.8$, 2.4 Hz, 1H), 3.53 (dd, $J = 12.5$, 3.0 Hz, 1H); $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta = 167.2, 150.9, 140.2, 134.7, 132.2, 130.2, 129.7, 128.9, 128.5, 127.3, 126.1, 124.2, 117.8, 116.9, 37.5, 36.8; m/z 309.1865 (M+1, C$_{19}$H$_{13}$ClO$_2$ requires 308.0604).

1-(4-Fluorophenyl)-1$H$-benzo[f]chromen-3(2$H$)-one (50c): White solid; m.p. 136-138 °C; IR (KBr/cm$^{-1}$): $\nu_{\text{max}} = 3061, 2955, 1733, 1654, 1516, 1347, 1270, 1173, 1072, 960, 851, 748; ^1H NMR (CDCl$_3$, 400 MHz): $\delta = 8.30$ (d, 8.5 Hz, 1H), 7.61 (d, $J = 8.0$ Hz, 1H), 7.51 (d, $J = 8.0$ Hz, 1H), 7.34-7.37 (m, 2H), 7.31 (d, 8.0 Hz, 1H), 7.24-7.27 (m, 2H), 7.05-7.10 (m, 2H), 4.80 (d, $J = 5.9$ Hz, 1H), 3.77 (dd, $J = 14.6$, 3.4 Hz, 1H), 3.16 (dd, $J = 14.2$, 2.5 Hz, 1H); $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta = 169.2, 161.0, 148.7, 137.3, 136.9, 132.4, 130.2, 129.3, 128.6, 127.4, 127.0, 125.8, 122.1, 118.6, 117.5, 116.3, 116.2, 37.5, 36.7; m/z 293.6101 (M+1, C$_{19}$H$_{13}$FO$_2$ requires 292.0900).

1-(4-Methoxyphenyl)-1$H$-benzo[f]chromen-3(2$H$)-one (50d): Yellowish solid; m.p. 135-136 °C; IR (KBr/cm$^{-1}$): $\nu_{\text{max}} = 3060, 2920, 1727, 1635, 1438, 1213, 1138, 1014, 958, 843, 742; ^1H NMR (CDCl$_3$, 400 MHz): $\delta = 7.79$ (d, $J = 8.2$ Hz, 2H), 7.77 (d, $J = 8.2$ Hz, 1H), 7.64-7.71 (m, 2H), 7.24 (d, $J = 8.6$ Hz, 1H), 7.09 (d, $J = 7.8$ Hz, 2H), 6.94 (d, $J = 8.7$ Hz, 2H), 4.78 (dd, $J = 6.6$, 3.2 Hz, 1H), 3.70 (s, 3H), 3.23 (dd, $J = 7.8$ Hz, 2H), 3.04 (dd, $J = 10.8$, 7.8 Hz, 2H), 2.42 (q, $J = 7.8$ Hz, 2H), 1.84 (d, $J = 6.8$ Hz, 3H), 1.10 (s, 3H); $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta = 169.2, 161.0, 148.7, 137.3, 136.9, 132.4, 130.2, 129.3, 128.6, 127.4, 127.0, 125.8, 122.1, 118.6, 117.5, 116.3, 116.2, 37.5, 36.7; m/z 293.6101 (M+1, C$_{19}$H$_{13}$FO$_2$ requires 292.0900).
12.6, 2.8 Hz, 1H), 3.08 (dd, J = 12.7, 3.4 Hz, 1H); $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta =$ 168.3, 157.0, 148.2, 134.8, 132.6, 131.3, 129.2, 128.4, 127.8, 127.6, 126.8, 125.4, 123.5, 1119.0, 117.3, 115.2, 114.1, 56.3, 37.9, 35.8; m/z 305.1133 (M+1, C$_{20}$H$_{16}$O$_3$ requires 304.1099).

1-(Thiophen-2-yl)-1$H$-benzo[f]chromen-3(2$H$)-one (50e): Sticky; IR (Film/cm$^{-1}$) $\nu_{max}$ = 2954, 1716, 1602, 1436, 1208, 1120, 1070, 960, 845, 745; $^1$H NMR (CDCl$_3$, 400 MHz): $\delta =$ 7.74 (d, J = 7.8 Hz, 1H), 7.64-7.71 (m, 2H), 7.38-7.52 (m, 3H), 7.20-7.30 (m, 1H), 7.08-7.14 (m, 2H), 4.01 (s, 1H), 3.92 (dd, J = 12.6, 2.2 Hz, 1H), 3.79 (dd, J = 12.6, 2.5 Hz, 1H); $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta =$ 169.1, 147.3, 144.2, 134.6, 128.6, 127.8, 127.0, 126.7, 126.3, 125.5, 125.3, 125.1, 123.3, 122.4, 37.6, 35.7; m/z 281.0592 (M+1, C$_{17}$H$_{12}$O$_2$S requires 280.0558).
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