Abstract

The content of this thesis consists of two types of research works. First part of the work covers the characterization of reaction intermediates in the direction of synthesis of xanthene derivatives which have diverse applications in medicinal chemistry and material science. It has been observed that xanthene moieties constitute the biologically active structural unit of a large number of natural products such as secalonic acid A, the eumitrin pigments, the beticolin toxins and the antibiotic xanthoquinodin A1. We have utilized heterogeneous and homogeneous catalytic systems for the preparation of 14-alkyl or aryl-14H-dibenzoxanthenes and the corresponding precursor intermediates, aryl-bis(2-hydroxy-1-naphthyl) methane (bisnaphthol) and its keto tautomers. For the first time, use of microwave radiation under solvent-free medium showed product selectivity against the different amount of solid acids for the preparation of dibenzoxanthenes and bisnaphthol derivatives. We also identified the existence of keto-enol tautomer for the first time towards the synthesis of dibenzoxanthene derivatives from the acid catalyzed two component reaction of 2-naphthol and aromatic aldehydes under reflux in methanol. The unstable keto isomers were fully characterized which gave a direct support for the proposed mechanism of dibenzoxanthene preparation. The bisnaphthol derivatives were also prepared in solution using homogenous catalyst at room temperature in less time. Another class of xanthene compounds, 1,8-dioxo-octahydroxanthene derivatives was prepared in neat condition using mechanochemical energy in presence of heterogeneous catalysts.

The second part includes the development of safer catalytic systems for the protection of carbonyl groups in the context of green chemistry. The protection of this group becomes a necessity in a multifunctional compound where the nucleophilic reaction is to be carried out at a different site other than the carbonyl group. The carbonyl group can be protected by converting it into different types of derivatives. We have utilized polymer supported Brønsted acid as reusable catalyst for the chemoselective preparation of 1,1-diacetate (acylal) from aldehyde group and deprotection of acylals to the carbonyl group in different condition. Similarly we have employed polyethylene glycol (PEG) as reusable catalyst and medium for
the efficient conversion of carbonyl compounds to oxime derivatives using microwave energy without addition of any acid or base catalyst. After that we have made a conversion of the 1,8-dioxo-octahydroxanthene compound, synthesized in the first part, to the corresponding oxime under microwave irradiation using PEG-600 as reusable reaction medium.

The content of the thesis is divided into five chapters.

Chapter 1: Review of Literature

This chapter illustrates about the oxygen containing heterocyclic xanthene derivatives which exhibit various medicinal as well as industrial applications. Two xanthene derivatives namely dibenzoxanthenes and xanthenediones have been extensively studied during the course of this work. Dibenzoxanthenes form the basic structural unit of various pharmaceutics and are used in photodynamic therapy and as antagonists for the paralyzing action of zoxazolamine. These compounds have also found applications in the industrial field as leuco-dye and in laser technologies and pH sensitive fluorescence materials for visualization of biomolecules. The second xanthene derivative of our interest, the xanthenediones has also been extensively examined by chemists because of their presence as structural moiety in numerous compounds having both medicinal and industrial value. Moreover the reaction intermediate leading to dibenzoxanthenes namely the aryl-bis(2-hydroxy-1-naphthyl) methane, often termed as bisnaphthols in short have been reported to possess non-steroidal pharmaceutical properties of anticancer, anti-inflammatory and anti-analgesic activity with large gastric tolerance. Some of them are also utilized as non-linear optical materials, enzyme mimetics, ion-selective electrodes or sensors, chiral ligands in organometallic chemistry, synthetic precursors for the formation of spirans and sometimes, as high-performance liquid chromatography stationary phases with some modifications. The detailed literature survey of the synthetic methodologies leading to dibenzoxanthenes and xanthenediones along with those of bisnaphthols were primarily emphasized.

The review also discusses the importance of carbonyl group protection in multistep reactions. Out of several carbonyl protecting groups, we were interested
to transform into 1,1-diacetates and oxime derivatives by considering the green chemistry approach. The stability of the acylals in neutral as well as basic media has made them an attractive alternative to the acetals. Acylals have varied industrial applications as cross-linking reagents for cellulose in cotton and activators in the composition of bleaching mixture used for the treatment of wine-stained fabrics. They are also utilized for the synthesis of 1-acetoxydienes and dihalovinyl acetates in Diels-Alder reactions, mainly the ones derived from α,β-unsaturated aldehydes. The oxime compounds are found to be potent intermediates for the synthesis of various nitrogen containing compounds and some heterocyclic moieties. Some oxime compounds possess medicinal properties as antimicrobial agents, pesticides, antioxidants, vasodilators, and inhibitors of P450. This chapter highlights the reported methods for synthesis of acylals using polymer supported solid acid catalysts and also the formation of oximes under solvent-microwave irradiation.

Furthermore, this chapter briefly presents about the general techniques wherein solid acid catalysts, polyethylene glycol and solvent-less organic reactions using microwave and mechanical energies were used during our work. In modern day research, solid acid catalysts have been extensively used as heterogeneous catalysts which have been the choice of interest in many research fields because of the reusability and eco-friendly factors. This property is very appreciating when the reactions are carried out at large scales basically in industries where disposal of the catalysts once the processes are over is a matter of environmental issue. Moreover, this brings down the cost of the entire system. Polyethylene glycols have also being exhibiting dual behavior both as reaction media and as phase transfer catalyst. The tunable property of this class of polymers upon adjustment of physical properties such as pressure, temperature has aided them to be easily recovered from the reaction mixture where they are used once the reaction is over. Merely decreasing the temperature leads to the precipitation of PEGs from the reaction mixture. PEGs have found enormous applications in varied fields of research. Solvent-free organic syntheses have become the interest of researchers and industrial workers because of the disposal issues of the toxic solvents used during bulk synthesis. Solvent-free mechanochemical grinding displays several advantages such as reduced pollution, minimization of energy consumption and
cost reduction. The replacement of the unnecessary and wasteful heating by microwave heating is considered to be quite effective for such syntheses as these leads to the uniform and homogeneous nature of the energy consumption by the reactants.

Chapter 2: Synthesis and characterization of Aryl-\textit{bis}(2-Hydroxy-1-Naphthyl) Methane and 14-Alkyl or Aryl-14\textit{H}-Dibenzoaxanthenes

This chapter is divided into two sections namely Section 2A and Section 2B.

Section 2A: Boron Sulfonic Acid (BSA) Catalyzed Selective Synthesis of Aryl-\textit{bis}(2-Hydroxy-1-Naphthyl) Methane and 14-Alkyl or Aryl-14\textit{H}-Dibenzoaxanthenes under Solvent-free Condition

This section of the chapter mainly contains the detailed synthesis of dibenzoaxanthenes (3) and its precursor intermediate, the bisnaphthols (2) using boron sulfonic acid (BSA) as the reusable solid acid catalyst in solvent-free condition (Scheme-1). The reactions have been carried out both via thermal as well as microwave heating of the reactants. The selectivity of the formation of products largely depends on the reaction condition. Thermal treatment in general leads to dibenzoaxanthenes whereas microwave irradiation seems to yield selectively the bisnaphthols. The reusability of the catalyst was tested and the activity was found to remain intact for four cycles giving almost the same yield. Moreover avoidance of solvents and the use of heterogeneous catalyst make the processes environment friendly and cost effective. The combination of the catalyst boron sulfonic acid and the process used make the reaction quite feasible. Monitoring of the progress of the reaction was done by thin layer chromatography.

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\begin{figure}
\centering
\includegraphics[width=\textwidth]{Scheme1.png}
\caption{Scheme-1}
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Section 2B: Investigation of Keto-enol Tautomers during the Synthesis of Aryl-bis(2-hydroxy-1-naphthyl) Methanes

In this section three Lewis acid catalysts, two heterogeneous, i.e., FeSO$_4$·7H$_2$O and CuSO$_4$·5H$_2$O and the homogeneous BF$_3$·OEt$_2$ have been studied for the synthesis of bisnaphthols (2). However, it was observed that FeSO$_4$·7H$_2$O was not that effective for the synthesis as CuSO$_4$·5H$_2$O in methanol under reflux condition. Moreover, BF$_3$·OEt$_2$ alone was not sufficient for the formation of bisnaphthols. The reactions seem to give satisfactory result only when acetic acid was used as promoter along with the BF$_3$·OEt$_2$ at room temperature in dichloromethane. Moreover for the first time, the isolation of the keto tautomer (1) of aryl-bis(2-hydroxy-1-naphthyl) methanes (2) was possible from the reactions of 2-naphthol and 4-chlorobenzaldehyde or 4-methylbenzaldehyde under reflux in methanol using CuSO$_4$·5H$_2$O as heterogeneous catalyst. These two keto isomers distinctly confirm the plausible mechanism for the dibenzoxanthene synthesis from aldehydes and 2-naphthol through the formation of keto-enol tautomerism (Scheme-2).

![Keto-enol tautomerism](image.png)

**Scheme-2**

In both the sections, all known and unknown products were characterized by melting points, $^1$H and $^{13}$C NMR, FT-IR, and elemental analysis techniques after purification via thin layer chromatography. The keto compounds (1) were identified with the help of DEPT, COSY along with the existing analysis.
Chapter 3: Mechanochemical Synthesis of 1,8-Dioxo-Octahydroxanthene Derivatives under Solvent Free Condition using Heterogenized Acid Catalysts

In this chapter, the synthesis of xanthenediones was investigated via mechanochemical grinding of aldehydes and 5,5-dimethyl-1,3-cyclohexanedione (dimedone) using polyaniline (PANI) supported Brønsted and Lewis acid catalysts (Scheme-3). Comparison between the unsupported catalysts, i.e. p-toluenesulfonic acid (p-TSA) and FeCl₃ with the supported ones over PANI was done for the synthesis. The supported catalysts were found to be better both in terms of time and yield. The selective formation of xanthenediones (4) was observed unlike in case of the unsupported ones. However, another catalyst, ferric nitrate nonahydrate was found to lose its activity when it was supported on montmorillonite K-10 as clayfen. The reaction was also carried out in different solvents taking p-chlorobenzaldehyde as the substrate in the model reaction. However, solvent-free condition was found to be the most effective. The change in the state of the reaction mixture during the progress of the reaction was distinctly visible. The reusability was also studied for the three supported catalysts. The activity almost remains unchanged for three consecutive cycles.

\[
\text{RCHO} + \overset{\text{Grinding Solvent-free}}{\text{Catalyst}} \rightarrow \overset{-\text{H}_2\text{O}}{\text{OH OH OH}} \rightarrow \overset{\text{OH OH OH}}{\text{R R R}} \overset{\text{OH OH OH}}{\text{R R R}}
\]

Where R = C₆H₅ (1a), 4-ClC₆H₄ (1b), 4-NO₂C₆H₄ (1c), 3-NO₂C₆H₄ (1d), 4-OHC₆H₄ (1e), 4-OHMeC₆H₄ (1f), 2-ClC₆H₄ (1g), 4-MeC₆H₄ (1h), 2-Naphthyl (1i)

Scheme-3

Chapter 4: Protection of carbonyl group using safer catalytic systems

The work in this chapter is divided in Section 4A and Section 4B.
Section 4A: Polymer-supported Brønsted Acid Catalyzed Chemoselective Protection of aldehydes to 1, 1-Diacetates and Deprotection to Carbonyl Group

This section basically deals with the chemoselective protection of aldehydes by converting them into 1,1-diacetates (acylals) at room temperature and deprotection to carbonyl group under reflux using poly(4-vinyl)pyridine supported sulfuric acid as catalyst in organic solvents (Scheme-4). The chemoselective nature of the catalyst along with reusability property makes this catalyst quite attractive to researchers and in industries. Moreover, acylals themselves are quite stable and have several practical utility. The reaction was studied both in dichloromethane and neat condition at room temperature. However, solvent-free media was found to be inferior as compared to the reactions in dichloromethane. In this case also, the catalyst was found to be reusable.

<table>
<thead>
<tr>
<th>RCHO</th>
<th>Ac₂O/ P4VP-H₂SO₄, DCM or neat/ r.t.</th>
<th>RCH(OAc)₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>R=alkyl, aryl</td>
<td>P4VP-H₂SO₄, CH₃CN, r.t. to 50 °C</td>
<td></td>
</tr>
</tbody>
</table>

Scheme-4

Section 4B: Dual Nature of Polyethylene Glycol under Microwave Irradiation for the Clean Synthesis of Oximes

In this section, polyethylene glycols have been studied for oxime synthesis from the reaction of equal molar amounts of carbonyl compound and hydroxylamine hydrochloride under microwave irradiation without addition of any acid or base catalyst (Scheme-5). However it was observed that among the three PEGs studied, i.e. 200, 400 and 600, the best result was obtained in 600. PEGs have been found to possess dual behavior, one as reaction media and the other as catalyst. PEGs have tunable property, which means that their property mainly depends on external factors like pressure, temperature and composition.
Chapter 5: Summary of the Present Work

This chapter summarizes the entire work described in this thesis.