CHAPTER VI
SUMMARY AND CONCLUSIONS

CHAPTER I

N-Bromosuccinimide (NBS) in Ionic Liquid: A Green System for Rapid Oxidation of 1,2-Diols, α-Hydroxyketones and Alcohols

Oxidation of 1,2-diols, α-hydroxyketones and alcohols is of paramount importance in organic synthesis because the reaction products (i.e., aldehydes/ketones and 1,2-diketones) are the key building blocks for the construction of complex organic molecules. In this chapter, we have reported a rapid and facile synthetic protocol for the oxidation of a variety of 1,2-diols, α-hydroxyketones and alcohols using NBS (N-bromosuccinimide) as an oxidant in 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim]BF₄) in the absence of any catalyst.

The appropriate reaction conditions were optimized by investigating the oxidation of hydrobenzoin with NBS in different ionic liquids, changing the molar ratio of substrate: NBS and by varying temperature. The reaction using 1: 2 molar ratio of substrate: NBS in [bmim]BF₄ at 70°C gave the best results. A number of hydrobenzoins, naphthoins and aliphatic 1,2-diols underwent oxidation to give the corresponding 1,2-diketones in high yields under these conditions (eq. 1). A variety of α-hydroxyketones also underwent oxidation to corresponding 1,2-diketones by using 1: 2 molar ratio of substrate: NBS (eq. 2).

\[
\begin{align*}
R=\text{CH} & \longrightarrow \text{CH} = R \\
\text{OH} & \quad \text{OH} \\
\text{NBS, [bmim]BF}_4 & \quad 70^\circ \text{C} \\
\rightarrow & \\
R=\text{C} & \longrightarrow \text{C} = R \\
\text{O} & \quad \text{O} \\
\end{align*}
\]

Subsequently, oxidation of different alcohols was attempted using NBS in [bmim]BF₄. Variously substituted primary and secondary aromatic alcohols underwent smooth oxidation to yield the corresponding carbonyl compounds in good yields under identical reaction conditions (eq. 3).
Reactions of primary aliphatic alcohols also resulted in the formation of their corresponding carbonyl compounds but reactions of secondary aliphatic alcohols resulted in the formation of corresponding bromides rather than the oxidized product (eq. 4).

CHAPTER II

Task Specific Ionic Liquid Mediated Synthesis of 4H-pyrans, 4H-pyrano[2,3-c]pyrazoles and 4H-benzo[g]chromenes

Multicomponent reactions (MCRs) have proven to be a very elegant and rapid way to access complex structures in a single synthetic operation from simple building blocks. MCRs show high atom economy and high selectivity. This chapter has been divided into three parts.

II.1: Synthesis of 4H-pyrans

In this part, we have reported an efficient and facile protocol for the synthesis of 4H-pyrans from aldehydes, malononitrile and ethyl acetoacetate/ acetylacetone utilizing 20 mol% of [bmim]OH as task specific ionic liquid at 50-60°C. The reaction of 4-chlorobenzaldehyde (1.0 mmol), malononitrile (1.0 mmol) and ethyl acetoacetate (1.0 mmol) was optimised by varying molar ratios of the TSIL [bmim]OH and reaction temperature. It was observed that 20 mol% of [bmim]OH was most effective for the multicomponent condensation reaction at 50-60°C in 30 min without any catalyst. Reactions of diversely substituted aldehydes were carried out under identical reaction conditions. All these aldehydes underwent cyclocondensation with malononitrile and ethyl acetoacetate to produce corresponding ethyl 6-amino-4-aryl-5-cyano-2-methyl-4H-pyran-3-carboxylates in excellent yields (eq. 5). Reactions of aromatic aldehydes with electron-withdrawing groups such as chloro, nitro proceeded faster and gave better yields compared to electron donating groups such as methoxy and methyl.
Replacement of ethyl acetoacetate by acetylacetone afforded corresponding 5-acetyl-2-amino-4-aryl-3-cyano-6-methyl-4H-pyran-2-ones in good yields. The ionic liquid could also be recycled without significant loss in the yields of products.

II.2: Syntheses of 4H-pyran[2,3-c]pyrazoles

In this part, we have reported the syntheses of a series of pyran[2,3-c]pyrazole derivatives via three component condensation of aldehydes, malononitrile and 5-methyl-2,4-dihydropyrazol-3-one under similar reaction conditions (Method A) (eq. 6). The synthesis of pyran[2,3-c]pyrazoles could also be achieved by four component condensation of aldehydes, malononitrile, ethyl acetoacetate and hydrazine monohydrate using [bmim]OH as task specific ionic liquid at 50-60°C (Method B) (eq. 7).

II.3: Synthesis of 4H-benzol[g]chromenes

In this part, the above protocol was further extended for the synthesis of 4H-benzol[g]chromenes by one pot condensation of equimolar amount of aromatic aldehydes, malononitrile and 2-hydroxy-1,4-naphthoquinone in the presence of [bmim]OH at 50-60°C. A wide range of diversely substituted aromatic aldehydes underwent this three component cyclocondensation with malononitrile and 2-hydroxy-1,4-naphthoquinone to produce corresponding 2-amino-4-aryl-5,10-dioxo-5,10-dihydro-4H-benzol[g]chromene-3-carbonitriles in good yield (eq. 8).
CHAPTER III

Efficient One Pot Syntheses of Dibenzo[\(a,i\)]xanthene-Diones and Evaluation of Their Antioxidant Activity

In this chapter, synthesis of 14-aryl-14\(H\)-dibenzo[\(a,i\)]xanthene-8,13-diones (III.1) and evaluation of their antioxidant activity has been reported (III.2).

III.1: Syntheses of 14-aryl-14\(H\)-dibenzo[\(a,i\)]xanthene-8,13-diones in aqueous media and task specific ionic liquid

Facile and convenient procedures for the synthesis of 14-aryl-14\(H\)-dibenzo[\(a,i\)]xanthene-8,13-diones have been reported in this chapter. The reaction employs one pot condensation of aldehydes, 2-hydroxynaphthalene-1,4-dione and 2-naphthol/ 2,7-dihydroxynaphthalene/ 2,6-dihydroxynaphthalene using catalytic amount of sulfuric acid in water under reflux. The products were obtained in excellent yields (Method A).

The same condensation could also be achieved using task specific ionic liquid, 1-butyl-3-methylimidazolium hydrogen sulfate ([bmim]HSO\(_4\)), which acts as an effective catalyst and reaction media for this transformation (Method B) (eq. 9). The reactions proceeded efficiently yielding the corresponding 14-aryl-14\(H\)-dibenzo[\(a,i\)]xanthene-8,13-diones in excellent yields.
III.2: Evaluation of antioxidant activities of dibenzo[α,ι]xanthene-8,13-diones by DPPH assay

Radical scavenging activity of the synthesized compounds was examined using DPPH (2,2-diphenyl-1-picrylhydrazyl) assay and compared with BHT (butylated hydroxy toluene) as standard. The disappearance of DPPH was measured spectrophotometrically at 517 nm using butylated hydroxy toluene (BHT) as standard. 0.8 µM/mL and 0.4 µM/mL solutions of 14-aryl-14H-dibenzo[α,ι]xanthene-8,13-diones were prepared using a mixture of methanol-acetone (1:1) (v/v) and % radical scavenging activity was calculated. These compounds were found to be efficient DPPH free radical scavengers. Among the synthesized dibenzoxanthene-diones, 2-/3-hydroxy-14-aryl-14H-dibenzo[α,ι]xanthene-8,13-diones showed potent DPPH radical scavenging activity, comparable to that of standard (BHT). Position of OH does not seem to have any significant effect on the free radical scavenging activity. Further, it was observed that the antioxidant property of dibenzoxanthene-diones was enhanced by electron donating groups in the aryl ring.

CHAPTER IV

Aqua Mediated Indium(III) Chloride Catalyzed Synthesis of Fused Pyrimidines and Pyrazoles

In this chapter, application of indium(III) chloride as catalyst has been examined for the synthesis of fused pyrimidines and pyrazoles and is divided into two parts.

IV.1: Synthesis of pyrimidine-2,4-diones, pyrimido[4,5-b]quinolines and pyrimido[2,3-d]pyrimidines

Pyridopyrimidines are known to exhibit promising biological and pharmacological activities. In this part, we have described a new and highly efficient protocol for the synthesis of pyrido[2,3-d]pyrimidines and novel pyrimidine-2,4-diones via three component condensation of aldehydes, 6-amino-1,3-dimethyl uracil and dimesdone using 20 mol% of indium(III) trichloride as catalyst in water under reflux. These novel pyrimidine-2,4-dione intermediates have been isolated for the first time and their structure has been confirmed by X-ray (Scheme I).
The optimised reaction conditions for three component condensation were also evaluated for condensation with other cyclic 1,3-dicarbonyl compounds, such as cyclohexane-1,3-dione, 5-methylcyclohexane-1,3-dione and indane-1,3-dione. Condensations with cyclohexane-1,3-dione and 5-methylcyclohexane-1,3-dione led to the formation of dihydropyrimido[4,5-b]quinolines. Condensations with indane-1,3-dione yielded the aromatized pyrido[2,3-d]pyrimidines in high yields.

**IV.2: Synthesis of pyrazolo[3,4-b]quinoline and pyrazolo[4,3-e]pyridine derivatives**

The pyrazolo[3,4-b]pyridine moieties represent important building blocks in both natural and synthetic bioactive compounds. In this part, synthesis of pyrazolo[3,4-b]quinolin-5-ones, pyrazolo[4,3-e]pyridin-5-ones, pyrazolo[3,4-b]pyridin-5(1H)-ones and pyrazolo[3,4-b]quinoline-5,10-diones have been reported via condensation of 3-methyl-1-phenyl-1H-pyrazol-5-amine, aromatic aldehydes and cyclic diketones like cyclohexane-1,3-dione, indane-1,3-dione, cyclopentane-1,3-dione and 2-hydroxy-1,4-naphthoquinone respectively, using 20 mol% of InCl$_3$ as catalyst in water under reflux (Scheme II).
CHAPTER V

An Expedient Four Component Domino Protocol for the Synthesis of Novel Benzo[a]phenazine Annulated Heterocycles and Their Photophysical Studies

In this chapter, synthesis of benzo[a]phenazine fused heterocycles has been reported by four component condensation. Their photophysical studies have also been reported.

V.1: Synthesis of novel benzo[a]phenazine annulated heterocycles

 Phenazine based compounds are the most abundant natural products, having myriad of biological functions. Fluorescent phenazine derivatives are also used as photo-sensitizers in photodynamic therapy (PDT). In this part, we report a new one pot, convergent, expedient sequential protocol for the synthesis of 16-aryl-benzo[a]chromeno[2,3-c]phenazin-1-ones and 15-aryl-benzo[a]cyclopenta[5,6]pyrano [2,3-c]phenazin-1-ones by the reaction of 2-hydroxynaphthalene-1,4-dione, 1,2-phenylenediamines, aromatic aldehydes and cyclic-1,3-dicarbonyl compounds like dimedone, cyclohexane-1,3-dione or cyclopentane-1,3-dione in the presence of p-TSA in polyethylene glycol (PEG-400) at 70°C in excellent yields (Scheme III). The protocol is environmentally benign, has high atom-economy and offers recyclability of the reaction media i.e. PEG-400. The structural assignment has been unambiguously confirmed by X-ray analysis.
V.2: Photophysical studies of novel benzo[α]phenazine annulated heterocycles

The spectral characteristics of the compounds such as absorption maxima ($\lambda_{\text{abs, max}}$), emission maxima ($\lambda_{\text{em, max}}$), extinction coefficient ($\varepsilon$) and Stokes shift were measured in chloroform. All the compounds, showed three absorption bands in the regions 370-385 nm, 390-405 nm and 445-465 nm. The increase in conjugation and increased electron density associated with chlorine groups in 4,5-dichlorobenzene-1,2-diamine led to a large bathochromic shift of absorption maxima in 12,13-dichloro-16-aryl-2,3,4,16-tetrahydro-1H-benzo[α]chromeno[2,3-c]phenazin-1-ones. A fluorescence excitation wavelength ($\lambda_{\text{ext}}$) of 370 nm was used for all the compounds. The influence of solvents on the fluorescence spectra of benzo[α]phenazine fused derivatives was investigated using different solvents such as chloroform, dichloromethane, dimethylsulphoxide and acetonitrile. The fluorescence spectra underwent significant red shift upon increasing solvent polarity. The Lippert-Mataga plot of the Stokes shift as a function of orientation polarizability ($\Delta f$) shows a good linear relationship, suggesting that specific solute-solvent interactions are involved, which is known to consist of several effects i.e., dipole-dipole interactions and dipole induced dipole interactions. Relative contribution of individual effect depends on the type of solvent used.