The present studies embodied in this dissertation focus on the use of green methodologies and reagents, namely ionic liquids, aqueous media and microwave towards the synthesis of catalytic reagents, some natural products and related organic compounds. These are arranged into four chapters.

Chapter I is further divided into three parts A, B and C. Synthesis of an acidic ionic liquid (Bmim)HSO₄ (4) is reported in section A. Microwave irradiations have been used effectively to decrease the reaction time for the synthesis of TSIL 1-butyl-3-methyl-imidazolium hydrogen sulphate (bmim)HSO₄ (4). It has been accomplished under solventfree conditions. The sequential representation of the reactions utilized is given as follows:

\[
\begin{align*}
\text{(a)} & \quad 30+10+10s, \text{MW} \\
\text{(b)} & \quad \text{NaHSO}_4, 10+10s, \text{MW}
\end{align*}
\]

Scheme I

Part B of Chapter I reports the synthesis of coumarin derivatives by the use of Bronsted acidic task specific ionic liquid (bmim)HSO₄ (4) as catalyst under solventfree conditions. Coumarins substituted and unsubstituted at the pyron ring has been prepared in good yields and high purity. The microwave irradiation as a source of heating has been employed to carry out the reaction. Reaction scheme and tabulated results are as shown below:
Summary

Scheme II

Table V: Results of (bmim)HSC catalyzed synthesis of 4-methyl substituted Coumarins

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Product</th>
<th>Time (min)</th>
<th>MW heating (h)</th>
<th>Thermal heating (h)</th>
<th>Yield (%)</th>
<th>m.p. (°)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HO OH</td>
<td>HO OH</td>
<td>2</td>
<td>12</td>
<td>81</td>
<td>62</td>
<td>182-184</td>
</tr>
<tr>
<td>OH</td>
<td>HO OH</td>
<td>9</td>
<td>20</td>
<td>85</td>
<td>65</td>
<td>280</td>
</tr>
<tr>
<td>HO OH</td>
<td>HO OH</td>
<td>10</td>
<td>15</td>
<td>79</td>
<td>58</td>
<td>242-244</td>
</tr>
<tr>
<td>H3CO OH</td>
<td>H3CO OH</td>
<td>3</td>
<td>5</td>
<td>65</td>
<td>45</td>
<td>129</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6</td>
<td>6</td>
<td>96</td>
<td>75</td>
<td>154</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5</td>
<td>6</td>
<td>83</td>
<td>64</td>
<td>129-131</td>
</tr>
</tbody>
</table>
Summary

The synthesis of coumarin derivatives unsubstituted at the pyron ring has also been accomplished under microwave irradiation.

\[
\begin{array}{ccc}
\text{X} & \text{OH} & \text{COOH} \\
\text{CH}_2 & \text{CHOH} & \text{COOH} \\
\end{array}
\rightarrow
\begin{array}{c}
\text{MW} \\
(bmim)\text{HSO}_4 \\
\end{array}
\rightarrow
\begin{array}{c}
\text{X} \\
\text{O} \\
\end{array}
\]

Scheme III

Table VI: Results of (bmim)HSO₄ catalyzed synthesis of 4-unsubstituted Coumarins under microwave irradiation

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Product</th>
<th>Time (min)</th>
<th>Yields (%)</th>
<th>m.p. (°)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HO OH</td>
<td>HO OH</td>
<td>3</td>
<td>78</td>
<td>210-212</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HO OCH₃</td>
<td>H₃C O</td>
<td>5</td>
<td>55</td>
<td>116-118</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HO OH</td>
<td>HO OH</td>
<td>10</td>
<td>69</td>
<td>265-266</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Part C of Chapter I incorporates the use of the prepared acidic task specific ionic liquid (bmim)HSO₄ (4), for a simple, elegant and green synthesis of 3,4-dihydropyrimidin-2-(1H)-ones in a one pot reaction under microwave irradiation, oil bath heating and grinding in a pestle mortar. The reaction scheme is as shown below and the results have been tabulated:

165
Summary

Scheme V

Table VII: Synthesis of 3,4-dihydropyrimidin-2-(1H)-ones catalyzed by (bmim)HSO₄

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Compound</th>
<th>Thermal Time (min)</th>
<th>Thermal Yield (%)</th>
<th>MW Time (min)</th>
<th>MW Yield (%)</th>
<th>Pestle Mortar Time (min)</th>
<th>Pestle Mortar Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="Image 1" /></td>
<td>10</td>
<td>96</td>
<td>2</td>
<td>90</td>
<td>10</td>
<td>89</td>
</tr>
<tr>
<td>2</td>
<td><img src="image2.png" alt="Image 2" /></td>
<td>10</td>
<td>94</td>
<td>2</td>
<td>92</td>
<td>10</td>
<td>87</td>
</tr>
<tr>
<td>3</td>
<td><img src="image3.png" alt="Image 3" /></td>
<td>15</td>
<td>96</td>
<td>3</td>
<td>79</td>
<td>15</td>
<td>75</td>
</tr>
</tbody>
</table>

166
Summary

4.

\[
\begin{array}{l}
\text{NO}_2 \\
\text{H}_3\text{C} \text{O} \text{C} \text{H}_3 \\
\text{N} \text{H} \\
\end{array}
\]

24

\[
\begin{array}{l}
\text{O} \\
\text{H}_3\text{C} \text{O} \text{C} \text{H}_3 \\
\text{N} \text{H} \\
\end{array}
\]

5.

\[
\begin{array}{l}
\text{NO}_2 \\
\text{H}_3\text{C} \text{O} \text{C} \text{H}_3 \\
\text{N} \text{H} \\
\end{array}
\]

25

\[
\begin{array}{l}
\text{O} \\
\text{H}_3\text{C} \text{O} \text{C} \text{H}_3 \\
\text{N} \text{H} \\
\end{array}
\]

6.

\[
\begin{array}{l}
\text{NO}_2 \\
\text{H}_3\text{C} \text{O} \text{C} \text{H}_3 \\
\text{N} \text{H} \\
\end{array}
\]

26

\[
\begin{array}{l}
\text{O} \\
\text{H}_3\text{C} \text{O} \text{C} \text{H}_3 \\
\text{N} \text{H} \\
\end{array}
\]

7.

\[
\begin{array}{l}
\text{OCH}_3 \\
\text{H}_3\text{C} \text{O} \text{C} \text{H}_3 \\
\text{N} \text{H} \\
\end{array}
\]

27

\[
\begin{array}{l}
\text{OH} \\
\text{H}_3\text{C} \text{O} \text{C} \text{H}_3 \\
\text{N} \text{H} \\
\end{array}
\]

8.

\[
\begin{array}{l}
\text{OH} \\
\text{H}_3\text{C} \text{O} \text{C} \text{H}_3 \\
\text{N} \text{H} \\
\end{array}
\]

27

167
**Summary**

<table>
<thead>
<tr>
<th>Structure</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Structure 29" /></td>
<td>15 96 2 92 15 86</td>
</tr>
<tr>
<td><img src="image" alt="Structure 30" /></td>
<td>15 97 2 91 10 92</td>
</tr>
<tr>
<td><img src="image" alt="Structure 31" /></td>
<td>15 96 2 90 10 87</td>
</tr>
<tr>
<td><img src="image" alt="Structure 32" /></td>
<td>20 84 5 65 15 69</td>
</tr>
<tr>
<td><img src="image" alt="Structure 33" /></td>
<td>25 82 - - 15 62</td>
</tr>
</tbody>
</table>
The developed methodology has been used for the preparation of bioactive molecule, Nitractin and Monastrol as shown below:

**Scheme VI: Synthesis of Nitractin**

**Scheme VII: Synthesis of Monastrol**

Chapter II has been subdivided into Part A and B. The former includes the synthesis of α-acyl amino amides through four component Ugi reaction. Room temperature ionic liquids have been explored as reaction media to determine the most suitable ionic liquid as given below:

**Table IX: Various solvents used for model Ugi reaction at 25 °C**

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Yields (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(bmim)PF₆</td>
<td>difficulty in product isolation</td>
</tr>
<tr>
<td>(bmim)BF₄</td>
<td>74</td>
</tr>
<tr>
<td>(bmim)Br (at 40 °C)</td>
<td>60</td>
</tr>
</tbody>
</table>
The results of the study are given in the tabular form:

<table>
<thead>
<tr>
<th>Reagents</th>
<th>Products</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>M.Pt (°)</th>
</tr>
</thead>
<tbody>
<tr>
<td>39 37 38</td>
<td>46</td>
<td>8</td>
<td>97</td>
<td>184-185</td>
</tr>
<tr>
<td>36 37 38</td>
<td>47</td>
<td>8</td>
<td>74</td>
<td>151-154</td>
</tr>
<tr>
<td>39 37 43</td>
<td>48</td>
<td>8</td>
<td>95</td>
<td>188-189</td>
</tr>
<tr>
<td>40 37 38</td>
<td>49</td>
<td>20</td>
<td>64</td>
<td>131-133</td>
</tr>
<tr>
<td>36 42 38</td>
<td>50</td>
<td>12</td>
<td>79</td>
<td>139-145</td>
</tr>
<tr>
<td>36 42 44</td>
<td>51</td>
<td>16</td>
<td>81</td>
<td>98-100</td>
</tr>
<tr>
<td>41 42 45</td>
<td>52</td>
<td>16</td>
<td>55</td>
<td>-</td>
</tr>
</tbody>
</table>
Recyclability of the reaction media was also studied:

\[
\begin{align*}
\text{NH}_2 & \quad \text{H}_3\text{CO} \\
\text{37} & \quad \text{39} \\
\text{O} & \quad \text{N} \\
\text{OH} & \quad \text{NC} \\
\text{38} & \quad \text{46}
\end{align*}
\]

Scheme VIII

Table XI: Recycling experiments in (bmim)BF₄

<table>
<thead>
<tr>
<th>Cycle</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1ˢᵗ</td>
<td>97</td>
</tr>
<tr>
<td>2ⁿᵈ</td>
<td>93</td>
</tr>
<tr>
<td>3ⁿᵈ</td>
<td>94</td>
</tr>
</tbody>
</table>

In continuation with the use of RTILs as reaction media for Ugi reaction, liquid phase library synthesis of α-acyl amino amides has been taken up in part B of chapter II. Task specific onium salt (TSOS) [3-(4-Aminobenzoyloxy)propyl]trimethylammonium tetrafluoro borate (58) has been prepared and used for the library synthesis. Sequence of reactions employed for the synthesis of onium salt is given in scheme below:

\[
\begin{align*}
\text{NH}_2 & \quad \text{Cl} & \quad \text{OH} \\
\text{53} & \quad \text{54} & \quad \text{a} \quad \text{55} \\
\text{N} & \quad \text{Cl} & \quad \text{OH} \\
\text{57} & \quad \text{56} & \quad \text{b} \quad \text{Cl} \\
\text{N} & \quad \text{Cl} & \quad \text{Cl} \\
\text{58} & \quad \text{56} & \quad \text{c} \quad \text{Cl} \\
\text{N} & \quad \text{Cl} & \quad \text{BF}_4 & \quad \text{d} \\
\text{58} & \quad \text{56} & \quad \text{Cl} \\
\end{align*}
\]

a) MW
Summary

b) DCC, DMAP, c) H₂, Pd/C
d) NaBF₄, H₂O

Scheme IX

The supported amine has first been used for the preparation of a single molecule (60) and subsequently for small library synthesis of four molecules (65-68).

Scheme X

a) (bmim)BF₄
b) MeOH, Et₃N
Chapter III has been arranged into part A and B. Part A comprises the synthesis of ionic liquid tagged proline based on the concept of ionic liquid supported synthesis (ILSS). The TSIL 1-(2-methyl-ethyl)-3-methyl imidazolium bromide (71) was synthesized through microwave irradiation of a mixture of 1-methyl imidazole and 1-bromo-2-(methylsulphonyl)ethane (69) followed by the anion exchange to obtain 1-(2-methyl-ethyl)-3-methyl imidazolium tetrafluoro borate (73). Methyl derivative of (2S, 4R)-hydroxyproline (70) was synthesized by

**Scheme XI**

a) (bmim)BF₄  
b) MeOH, Et₃N
treated with thionyl chloride and methanol. The crude product was subjected to N-Boc protection.

Coupling of ionic liquid mesylate in toluene and DMF, in the presence of sodium hydride, with N-tert-butyl-carbonyl-(2S,4R)-hydroxyproline methyl ester (72) provided ionic liquid supported proline (74) with protected amine and acid functionalities. (2S,4R)-1-tert-butyl-2-methyl-4-(2-(3-methylimidazolium)ethoxy)pyrrolidine-1,2-dicarboxylate tetrafluoro borate (74) was first Boc deprotected using TFA/DCM followed by hydrolysis with NaOH to yield the ionic liquid supported proline (75).

\[
\begin{align*}
&\text{Br} \quad \text{O} & & \text{O} \\
&\text{a) 1-Methyl imidazole, MW} \\
&\text{H}_3\text{C} \quad \text{N} & & \text{O} & & \text{S} & & \text{O} \quad \text{CH}_3 \\
&\text{71} & & \text{Br}^- \\
&\text{c} \\
&\text{H}_3\text{C} \quad \text{N} & & \text{O} & & \text{S} & & \text{O} \quad \text{BF}_4^- \\
&\text{73} \\
&\text{d} \\
&\text{H}_3\text{C} \quad \text{N} & & \text{O} & & \text{O} \quad \text{BF}_4^- \\
&\text{O} & & \text{O} & & \text{O} & & \text{N} & & \text{O} & & \text{BF}_4^- \\
&\text{74} \\
&\text{e} \\
&\text{H}_3\text{C} \quad \text{N} & & \text{O} & & \text{O} & & \text{N} & & \text{O} & & \text{BF}_4^- \\
&\text{75}
\end{align*}
\]
b) (i) CH₃COCl, MeOH; (ii) (t-Boc)₂O, (C₂H₅)₃N, DCM

c) NaBF₄, H₂O

d) NaH, DMF, Toluene

e) (i) TFA, DCM; (ii) aqueous NaOH, dil HCl

**Scheme XII**

Part B of chapter III embodies the use of ionic liquid supported proline for asymmetric aldol reaction. Different imidazole based ionic liquids were screened as the solvent to carry out the reaction and to check the stereoselectivities for the model reaction between p-nitrobenzaldehyde and acetone.

![Scheme XII](image)

**Table XII: Supported Ionic Liquid Proline catalyzed Aldol reaction in different solvents**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>DMSO</td>
<td>98</td>
<td>71</td>
</tr>
<tr>
<td>2.</td>
<td>(bmim)Br</td>
<td>92</td>
<td>79</td>
</tr>
<tr>
<td>3.</td>
<td>(bmim)BF₄</td>
<td>67</td>
<td>77</td>
</tr>
<tr>
<td>4.</td>
<td>(bmim)PF₆</td>
<td>95</td>
<td>80</td>
</tr>
<tr>
<td>5.</td>
<td>(bmim)NT₂₂</td>
<td>54</td>
<td>62</td>
</tr>
<tr>
<td>6.</td>
<td>Water</td>
<td>no reaction</td>
<td>-</td>
</tr>
</tbody>
</table>

The reaction of p-nitrobenzaldehyde and p-chlorobenzaldehyde was also carried out with cyclic ketones i.e. cyclohexanone and cyclopentanone in (Bmim)PF₆. The results of the study are presented in Table XIII.

**Table XIII: Supported Ionic Liquid Proline catalyzed aldol reaction of different aromatic aldehydes with cyclic ketones in (bmim)PF₆**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde</th>
<th>Ketone</th>
<th>Product a</th>
<th>Yield (%)</th>
<th>de</th>
</tr>
</thead>
</table>

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Catalyst recycling was also checked in the chosen ionic liquid solvent using p-nitrobenzaldehyde and cyclohexanone as the substrates.

Table IX: Recycling studies of Supported Ionic Liquid Proline catalyzed Aldol reaction between p-nitrobenzaldehyde and cyclohexanone

<table>
<thead>
<tr>
<th>Entry</th>
<th>Recycle</th>
<th>Yield (%)</th>
<th>de</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>1st</td>
<td>98</td>
<td>82:18</td>
</tr>
<tr>
<td>2.</td>
<td>2nd</td>
<td>98</td>
<td>79:21</td>
</tr>
<tr>
<td>3.</td>
<td>3rd</td>
<td>96</td>
<td>66:34</td>
</tr>
</tbody>
</table>
Chapter IV consist of further Part A, B and C. Synthesis of 2-(1Z)-(3-hydroxy-3,7-dimethylocta-1,6-dienyl)-1,4-benzenediol (85) found in the roots bark of *Cordia alliodora*, has been included in part A. Compound (85) showed anti fungal properties against the pythogenic mold *Cladosporium cucumerinum*. A short synthesis of titled compound (85) has been carried out by making use of MW irrigations and water as solvent in key steps as shown below:

\[ \text{Salicylaldehyde (86) was oxidised using K}_2\text{S}_2\text{O}_8 \text{ under aqueous condition to get 2,5-dihydroxybenzaldehyde. 2,5-Dihydroxybenzaldehyde (87) was subjected to methylation using dimethyl sulphate under MW irradiation to get white crystals of 85.} \]

f) \text{aq.NaOH, K}_2\text{S}_2\text{O}_8 

g) \text{aq.NaOH, DMS, MW} 

h) \text{aq.NaOH, MW, 7-methyl-5hepten-2-one} 

i) \text{MeMgl, CeCl}_3\text{, THF} 

j) \text{BBr}_3\text{, DCM, }-78^\circ\text{C} 

**Scheme XV**

Salicylaldehyde (86) was oxidised using K\textsubscript{2}S\textsubscript{2}O\textsubscript{8} under aqueous condition to get 2,5-dihydroxybenzaldehyde. 2,5-Dihydroxybenzaldehyde (87) was subjected to methylation using dimethyl sulphate under MW irradiation to get white crystals of
2,5-Dimethoxybenzaldehyde (88) which upon aldol condensation with 6-Methylhet-5-en-2-one using aq.NaOH under MW yielded 2-(1Z)-(7-methyl-3-oxoocta-1,6-dienyl)-1,4-dimethoxybenzene. MeMgl in THF on Grignard reaction 2-(1Z)-(7-methyl-3-oxoocta-1,6-dienyl)-1,4-dimethoxybenzene (89) gave 1,2-addition product (90). Finally deprotection of (89) using BBr₃ in DCM at -78° furnished the title compound (85).

Synthesis of 1-(3'-methoxypropanoyl)-2,4,5-trimethoxybenzene (91), a compound reported to have antifungal and larvicidal activity against the phytopathogenic mold Calosporium cucumerinium and larvae of yellow fever transmitting mosquito Aedes aegypti, respectively, has been reported in part B of chapter IV. Rate acceleration has been obtained through the use of microwave irradiation. Water has been used as solvent in a number of steps.

\[ \text{a) } \text{Na}_2\text{Cr}_2\text{O}_7, \text{H}_2\text{SO}_4, \text{H}_2\text{O} \]
\[ \text{b) } (\text{CH}_3\text{CO})_2\text{O} \]
\[ \text{c) } \text{HCl}, \text{C}_2\text{H}_5\text{OH} \]
\[ \text{d) } \text{DMS}, \text{NaOH}, \text{H}_2\text{O} \]
\[ \text{e) } \text{K}_2\text{S}_2\text{O}_8, \text{CH}_3\text{CN}, \text{I}_2, \text{MW} \]
\[ \text{f) } ^\text{OMe}, \text{Pd(OAc)}_2 (1 \text{ mol } \%), \text{NaOAc}, (\text{Bmim})\text{Br} \]
Oxidation of hydroquinone (92) with sodium dichromate led to the formation of quinine (93) crystals which on treatment with excess of acetic anhydride gave 1,2,4-triacetoxybenzene (94). 1,2,4-Trihydroxybenzene (95) was obtained through acid hydrolysis of 1,2,4-triacetoxybenzene and further subjected to methylation to get 1,2,4-trimethoxybenzene (96) after treatment with dimethyl sulphate in aqueous NaOH. Iodination of 1,2,4-trimethoxybenzene (96) was done using I₂ and K₂S₂O₈ in acetonitrile under microwave irradiation. The Heck reaction of 1-iodo-2,4,5-trimethoxybenzene (97) using Pd(OAc)₂ as catalyst and (Bmim)Br as solvent, with methyl acrylate led to the formation of methyl 2,4,5-trimethoxy cinnamate (98). The Mg/ZnCl₂ mediated selective reduction of C=O in aqueous media led to the formation of the final compound (91).

**Part C of chapter IV** embodies the synthesis of 1,2,4-trihydroxynonadecane which has been obtained from unripe fruits of *Persea americana*. The compound showed activity against six human tumor cell lines in culture and showed selectivity for prostate adenocarcinoma cells. Synthesis of compound (99) has been carried out in good yield using known reactions as shown below:

(a) PCC, Silica, MW

(b) Mg, diethyl ether, \( \text{Br} \)}
Hexadecanol (104) was oxidized to 1-hexadecanal using PCC doped on silica gel under microwave irradiation. Grignard reaction of allylmagnesium bromide with 1-hexadecanal (105) gave nonadec-1-ene-4-ol (106). Nonadec-1-ene-4-ol (106) was subjected to KIO₃ catalyzed dihydroxylation of the double bond to obtain the title compound (99).

Chiral analogue of 1,2,4-trihydroxynonadecane has also been synthesized by enzymatic resolution of racemic nonadec-1-ene-4-ol using *Candida cylindracea* lipase.

Scheme XVII

\[
\begin{align*}
\text{OH} & \quad \text{a} \quad \text{OH} \\
14 & \quad 14 \quad 14
\end{align*}
\]

(a) *Candida cylindracea*, diethyl ether,
(b) ADβ, (bmim)BF₄/t-BuOH

Scheme XVIII

180