2.1 Introduction
The removal of a carboxyl group (-COOH), usually in the form of carbon dioxide is termed as decarboxylation. It is a fundamental organic transformation widely used in synthesis or mechanistic investigation of organic compounds [Patai (1969)]. Some salient applications of decarboxylation reactions are briefly described below:

2.2 Significance of decarboxylation
2.2.1 Role in biosynthetic pathways
In the biochemical milieu, decarboxylation is a ubiquitous step for transformation of amino acids into various other secondary metabolites using specific enzymes termed decarboxylases [Liu and Zhang (2006)]. More importantly, nature has also employed decarboxylation as a central tool for linking metabolic pathways like glycolysis and citric acid cycle, whereby, pyruvate is decarboxylated into acetyl CoA which subsequently enters the citric acid cycle (Figure 1) [Nelson and Cox (2009)]. In this way, it commits pyruvate to enter the citric acid cycle, where it is either used as a substrate for oxidative phosphorylation, or is converted to citrate for export to the cytosol.

![Figure 1](image_url). Decarboxylation as a central tool for linking two different metabolic pathways
2.2.2 Decarboxylation as an enabling tool for synthesis of bioactive compounds and carbon chain shortening

Decarboxylation has also been extensively employed in organic synthesis for accessing a wide range of biologically active compounds. It constitutes one of the final steps for several classical transformations like Reissert, Fischer and Rees-Moody reactions for synthesis of 2-unsubstituted indoles (Scheme 1) [Jones and Chapman (1993)]. Similarly, the well-known Knoevenagal-Doebner [Dale and Hennis (1958)] and Perkin condensation [Solladie et al. (2003)] also involve a removal of carboxyl function for synthesis of styrenes and stilbenes respectively (Scheme 1). On the other hand, decarboxylation is also one of the few reactions enabling cleavage of C-C bonds [Payette and Yamamoto (2008)] which are otherwise quite stable to synthetic manipulations.

![Scheme 1](image)

Scheme 1. Utility of decarboxylative transformations in synthesis of biologically important compounds i) Indoles, ii) Styrenes, iii) Stilbenes

2.2.3 Decarboxylative coupling as a new strategy for C-C bond formation

Recently, decarboxylation has emerged as a pivotal element to design conceptually newer carbon-carbon bond forming strategies [Baudoin (2007)]. The immense interest in such decarboxylative couplings is mainly because carboxylic acids offer an easily available and economical alternative to the expensive organometallic/organohalide reagents conventionally used for cross coupling reactions. Thus, pioneering efforts by Meyers et al. has lead to the utilization of aromatic acids as novel organohalide equivalents for eventual Heck type coupling with olefins [Myers et al. (2002); Tanaka and Myers (2004)]. On the other hand, Gooßen and others have shown that benzoic acids can also serve as versatile
organometallic reagent equivalents for efficient coupling with aryl halides [Gooßen et al. (2006); Gooßen et al. (2007)], diaryliodonium salts [Becht and Drian (2008)] and indoles [Cornella et al. (2009)] etc. (Scheme 2).

Scheme 2. Decarboxylation based C-C coupling using carboxylic acid synthons as i) organohalide equivalents, ii) organometallic equivalents

In view of their above mentioned importance, there has been an upsurge of interest in developing newer decarboxylation approaches. However, the removal of carboxyl group has remained one of the most difficult transformations often requiring prior activation by metal catalysts as well as the use of harsh organic bases [Cohen and Schambach (1970); Lisitsyn (2007)]. In particular, the seminal work of Shepard et al., wherein, a combination of copper catalyst and quinoline provided a quintessential reagent system for decarboxylation has remained a prominent hallmark [Shepard et al. (1930)]. Later on, some variants of above protocol as well as other metal promoted methodologies have also been developed for decarboxylative synthesis of important targets like indoles, styrenes, stilbenes and aromatic derivatives.

2.3 Reported methods for decarboxylation reactions

A brief description of the prevalent approaches for decarboxylation of heteroaromatic, cinnamic acid and aromatic carboxylic acid derivatives is presented below:

2.3.1 Decarboxylation of N-heteroaryl carboxylic acids

Jones et al. used a combination of quinoline/Cu salt in sealed tube for decarboxylation of indole-2-carboxylic acids under microwave irradiation (Scheme 3) [Jones and Chapman (1993)].
Similarly, the decarboxylation of indole-2-carboxylic ester (Ethyl 3-cyano-1-methoxy-1H-2-indolecarboxylate) has been accomplished through a two step sequence involving initial hydrolysis using LiOH followed by quinoline/Cu promoted decarboxylation of resulting indole-2-carboxylic acids (Scheme 4) [Selvakumar and Rajulu (2004)]. The above protocol was further applied towards the total synthesis of some bioactive alkaloids possessing 2-unsubstituted indole framework.

In the same vein, Gan et al. employed quinoline/Cu combination for decarboxylation of indole-2-carboxylic acid which was in turn obtained from Fischer indole cyclization approach (Scheme 5) [Gan et al. (1997)]. The resulting indole was further used for total synthesis of Tryprostatin A, a potential inhibitor of indoleamine 2,3-dioxygenase.

On the other hand, a silver catalyzed protocol for protodecarboxylation of various heteroaromatic acids has been reported using Ag₂CO₃/AcOH (Scheme 6) [Lu et al. (2009)].
Maehara et al. disclosed a Pd catalyzed decarboxylation of indole-2-carboxylic acid and demonstrated its application for regioselective synthesis of 3 vinylated indoles (Scheme 7) [Maehara et al. (2008)].

\[
\text{Scheme 7}
\]

### 2.3.2 Decarboxylation of Cinnamic acids

Walling et al. investigated the decarboxylation of substituted cinnamic acids using various copper salts and found that copper powder in boiling quinoline accelerated the decarboxylation of cinnamic acids into corresponding styrenes (Scheme-8) [Walling and Wolfstrin (1947)].

\[
\text{Scheme 8}
\]

In another report, the antimitotic \textit{cis}-combetastatin A-4 was synthesized via decarboxylation of corresponding \(\alpha\)-phenyl cinnamic acid \((E)-3-(3'\text{-Hydroxy}-4'\text{-methoxyphenyl})-2-(3''\text{-hydroxy}-4''.5''\text{-trimethoxyphenyl})\text{-prop-2-enoic acid})\) using a combination of Cu/quinoline (Scheme 9) [Gaukroger et al. (2001)].

\[
\text{Scheme 9}
\]

An enzymatic decarboxylation of 4-hydroxy cinnamic acids into 4-vinylphenol was achieved using the \textit{para}-hydroxycinnamic acid decarboxylase (Scheme 10) [Bassat et al. (2007)].
Nomura et al. reported the decarboxylation of hydroxylated cinnamic acids into corresponding styrenes using amine bases (Scheme-11) [Nomura et al. (2005)].

A microwave assisted decarboxylation of hydroxy substituted α-phenyl cinnamic acids into corresponding stilbenes using a combination of methylimidazole and piperidine has been disclosed (Scheme 12) [Kumar et al. (2007)].

Similarly, DBU promoted decarboxylation of hydroxyl cinnamic acids has been reported using basic aluminium oxide as solid support (Scheme 13) [Bernini et al. (2007)].
2.3.3 Decarboxylation of aromatic acids

The decarboxylation of ortho/para nitro substituted phenyl acetic acids was achieved using \( \text{K}_2\text{CO}_3 \) in DMF (Scheme-14) [Bull et al. (1996)].

\[
\text{Scheme 14}
\]

The photodecarboxylation of acetoyl substituted phenyl acetic acids was investigated in water:AcCN (1:1) solvent system and a photolytic mechanism was proposed (Scheme 15) [Xu and Wan (2000)]. Further, it was hypothesized that \( \alpha \)-arylpropionic acids, constituents of nonsteroidal anti-inflammatory drugs (NSAIDs) might also be metabolized via an analogous oxidative decarboxylative pathway.

\[
\text{Scheme 15}
\]

On the other hand, decarboxylation of 3,5-dichloro-4-hydroxy-benzoic acid into the pharmaceutically important 2,6-dichlorophenol was achieved using \( \text{Cu}_2\text{O}/\text{quinoline} \) (Scheme-16) [Mukhopadhyay and Chandalia (1999)].

\[
\text{Scheme 16}
\]

A catalytic protocol for decarboxylation of 4-hydroxy substituted benzoic acids has been reported using \( \text{Pd} \) in combination with diphosphine ligand (Scheme 17) [Magro et al. (2009)].

\[
\text{Scheme 17}
\]
Similarly, a palladium catalyzed decarboxylation of various bis-ortho-substituted aromatic acids has been developed and the methodology was also found to be applicable on hindered carboxylic acids (Scheme 18) [Dickstein et al. (2007)].

![Scheme 18](image)

In another report, the decarboxylation of naphthyl carboxylic acid was achieved using Pd/C under hydrothermal conditions (Scheme 19) [Matsubara et al. (2004)].

![Scheme 19](image)

Recently, Gooßen et al. found that a silver based catalyst system was effective in promoting protodecarboxylation of ortho substituted aromatic acids (Scheme 20) [Gooßen et al. (2009)].

![Scheme 20](image)

On the other hand, Meyers et al. developed a palladium catalyzed sequential decarboxylation of aromatic acids which was followed by a Heck type coupling with alkenes (Scheme 21) [Myers et al. (2002)]. The use of ortho-substituted benzoic acids as
substrates besides Ag$_2$CO$_3$ as base and DMSO (5% v/v) in DMF as solvent was found to be critical for success of above reaction.

In a complementary strategy, Gooßen et al. utilized nitro substituted benzoic acids as organometallic reagent equivalents which under palladium catalysis undergo decarboxylation-coupling with aryl halides to furnish the biaryls (Scheme 22) [Gooßen et al. (2007)].

![Scheme 22](image)

In view of the above literature precedents, it would be apparent that a majority of the prevalent decarboxylation approaches employ harsh reaction conditions involving metal catalysts and/or strong bases. For instance, the rampant use of copper/quinoline based decarboxylation approach is known to generate environmentally hazardous residues besides sometimes providing a poor to moderate yield of desired product due to the propensity for concomitant side reactions [Locatelli et al. (2005)]. In addition, it also entails an extra step involving neutralization with an excess of acid. Although there have been noteworthy efforts to devise more benign decarboxylation conditions with various improvements, however, these have also been found to be constrained by an indispensable usage of either different metals like silver [Gooßen et al. (2009)], palladium [Dickstein et al. (2007)], mercury [Moseley and Gilday (2006)] or specialized techniques involving supercritical water-Pd/C etc [Matsubara et al. (2004)]. On the other hand, the biocatalytic methods exhibit limited generality. In this context, it would be highly desirable if a mild and metal-free methodology for decarboxylation of a wide range of substrates could be devised.

2.4 Ionic Liquids

The emergence of new enabling technologies often provides a fresh stimulus to approach longstanding problems. Ionic liquids have recently emerged as one of the leading reaction medium besides being a central element of green chemical practices [Sheldon (2005); Welton (1999)]. As discussed in the introduction section, the usage of room temperature
ionic liquids (RTIL’s) have provided a beneficial approach due to several attendant benefits like low volatility, high thermal stability besides their remarkable ability to promote a wide array of organic transformations [Wasserscheid and Welton (2008); Welton (1999)]. In addition, there has been much recent interest in developing “catalyst free” organic transformations in neat ionic liquids, wherein, the classical necessity of an additional metal or acid/base catalyst stands removed [Meciarova et al. (2007); Parvulescu and Hardacre (2007)].

2.5 Results and Discussion

In order to realize the objective of developing a mild and metal-free decarboxylation approach, it was envisaged to explore the catalytic ability of ionic liquids [Wasserscheid and Welton (2008)]. To the best of our knowledge, room temperature ionic liquids have not been systematically explored to promote decarboxylative transformations apart from some initial mechanistic reports [Oswald et al. (2005); Wong and Wu (2006)]. Initially, indole-2-carboxylic acid was chosen as the model substrate, as these constitute one of the most useful precursors for synthesis of immensely important 2-unsubstituted indole scaffolds [Jones and Chapman (1993)]. Consequently, indole-2-carboxylic acid (1a) was treated with ionic liquid 1-butyl-3-methylimidazolium hydroxide [bmim]OH (Table 1, entry 1) under microwave irradiation (MW).

The above reaction condition was found to provide the expected 1b (60% yield) at 240°C optimized temperature. Subsequently, various other ionic liquids were screened (Table 1) for further increasing the reaction performance. Interestingly, the use of neutral ionic liquid 1-hexyl-3-methylimidazolium-

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ionic liquid</th>
<th>reaction time [min]</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1-butyl-3-methylimidazolium hydroxide</td>
<td>25</td>
<td>60</td>
</tr>
<tr>
<td>2</td>
<td>1-methylimidazolium p-toluensulfonic acid</td>
<td>25</td>
<td>49</td>
</tr>
<tr>
<td>3</td>
<td>1-butyl-3-methylimidazolium hexafluorophosphate</td>
<td>25</td>
<td>traces</td>
</tr>
<tr>
<td>4</td>
<td>1-butyl-3-methylimidazolium tetrafluoroborate</td>
<td>25</td>
<td>5</td>
</tr>
<tr>
<td>5</td>
<td>1-butyl-3-methylimidazolium chloride</td>
<td>25</td>
<td>72</td>
</tr>
<tr>
<td>6</td>
<td>1-butyl-3-methylimidazolium bromide</td>
<td>20</td>
<td>74</td>
</tr>
<tr>
<td>7</td>
<td>1-hexyl-3-methylimidazolium bromide</td>
<td>20</td>
<td>79</td>
</tr>
<tr>
<td>8</td>
<td>1-methylimidazole</td>
<td>40</td>
<td>nd</td>
</tr>
<tr>
<td>9</td>
<td>1-hexyl-3-methylimidazolium bromide + water</td>
<td>15</td>
<td>88</td>
</tr>
</tbody>
</table>

*aCEM monomode microwave. bWater (8 mmol). cIsolated yield. dNot detected.

General condition: 1a (1.2 mmol), ionic liquid (1.5 ml) under MW for 15–40 min (250W, 240 °C)
bromide [hmim]Br (Table 1, entry 7) was found to provide expected 1b in comparatively superior yield (79%) as compared to that obtained with basic and acidic ionic liquids. In the course of our further attempts to enhance the reaction yield it was reasoned that decarboxylation might have been hindered by the well known tendency of ionic liquids to trap carbon dioxide [Wahelgren et al. (2006)]. However, application of simultaneous evacuation using either a vacuum assembly or nitrogen purging to aid the release of liberated carbon dioxide also proved futile. Thereafter, it was planned to use ionic liquid in conjunction with water as some recent reports had disclosed the beneficial role of such a combination for various organic transformations [Liao et al. (2005); Zhao et al. (2006)]. It was fascinating to note that addition of water (Table 1, entry 9) did indeed improve the reaction performance as 1b was obtained in 88% yield in a reduced reaction time of 15 min at 240°C. The presence of water might have favored decarboxylation as it allowed increased mass transfer of an otherwise viscous reaction mixture [Liao et al. (2005); Zhao et al. (2006)]. Moreover, the widely recognized hydrophilic nature of above ionic liquid [Welton (1999)] apparently prevented any appreciable loss of water upon MW irradiation, thereby, preventing any adverse effect on reaction performance. On the other hand, a further increase in amount of water didn’t help as it prevented the reaction mixture to attain required temperature for decarboxylation.

It is also worthwhile to mention that after work up, the recovered ionic liquid was reused as such for three consecutive cycles to afford 88%, 82% and 75% yield of 1b, thereby, demonstrating the recyclability of ionic liquid for above decarboxylation. In order to ascertain the specific role of microwave irradiation, the developed decarboxylation of 1a was also attempted under conventional heating in oil bath at similar temperature (240°C), however, the expected 1b was obtained in only 31% yield after 6 hr of heating along with some unreacted starting material besides blackening of reaction mixture. The foregoing result highlights the utility of microwave irradiation in ionic liquid assisted decarboxylation.

Subsequently, the applicability of developed method on various other N-heteroaryl carboxylic acids was evaluated. It would be apparent from Table 2 that the above protocol was effective for decarboxylation of diverse nitrogen containing heteroaryl carboxylic acids possessing indole (Table 2, entries 2, 5-6), indazole (Table 2, entry 3) and quinoline (Table
2, entry 4) moieties under metal-free conditions. Importantly, the developed protocol also facilitated a useful one pot hydrolysis-decarboxylation of indole carboxylic esters (Table 2, entries 5-6) as such transformations are usually carried out via a two step base induced hydrolysis-decarboxylation approach. Further the above result assumes significance as the total synthesis of alkaloid natural products often involves the removal of a carboxylic ester moiety from indole nucleus [Gan et al. (1997); Selvakumar and Rajulu (2004)]. On the other hand, the indole-3-phenyl acetic acids (Table 3, entries 7-9) were also rapidly

### Table 2. Decarboxylation of N-heteroaryl carboxylic acids using neat [hmim]Br under MW\(^a\) without any catalyst.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate (a)</th>
<th>Reaction time [min]</th>
<th>Product (b)</th>
<th>Yield(^b) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>15</td>
<td></td>
<td>88</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>15</td>
<td></td>
<td>83</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>15</td>
<td></td>
<td>85</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>15</td>
<td></td>
<td>86</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>15</td>
<td>1b</td>
<td>75</td>
</tr>
<tr>
<td>6</td>
<td>Me</td>
<td>15</td>
<td></td>
<td>41</td>
</tr>
</tbody>
</table>


### Table 3. Decarboxylation of indole indole-3-acetic acids using neat [hmim]Br under MW\(^a\) without any catalyst.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate (a)</th>
<th>Reaction time [min]</th>
<th>Product (b)</th>
<th>Yield(^b) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td></td>
<td>15</td>
<td></td>
<td>82</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td>15</td>
<td></td>
<td>90</td>
</tr>
<tr>
<td>9</td>
<td></td>
<td>15</td>
<td></td>
<td>49</td>
</tr>
</tbody>
</table>

\(^a\) CEM monomode microwave. \(^b\) Yield of pure isolated product. General condition: substrate 7a-9a (1.2 mmol), [hmim]Br (1.5 ml), water (8 mmol); MW: (250W, 240 °C).
decarboxylated using these conditions.

Having developed a neat [hmim]Br/water promoted metal free decarboxylation protocol for N-heteroaryl carboxylic acids (Table 2-3, entries 1-9), it was decided to extend the same towards decarboxylation of \(\alpha,\beta\)-unsaturated aryl carboxylic acids \textit{i.e} hydroxycinnamic acids as these are precursors of various industrially and medicinally important hydroxy styrenes [Crouzet \textit{et al.} (1997)]. It may be mentioned that a few protocols [Bernini \textit{et al.} (2007); Nomura \textit{et al.} (2005)] disclose such a synthesis of hydroxystyrenes, however, these have been constrained either by the susceptibility of product styrenes towards polymerization or usage of strong organic bases. Thus, a mixture of 4-hydroxy-3,5-dimethoxy cinnamic acid (10a) and neat [hmim]Br/water was irradiated under MW (150°C optimized temperature, 30 min) to provide canolol (10b), an anticancer compound [Cao \textit{et al.} (2008)] in 34% yield. Similarly, 4-hydroxy-3-methoxy cinnamic acid (11a) also provided the corresponding styrene 11b in 36% yield. In order to further enhance the yield of hydroxystyrenes (10b-11b), the addition of a small amount of base was envisaged as such a combination has been earlier found to improve the performance of various ionic liquid mediated transformations [Meciarova \textit{et al.} (2007)]. Consequently, 10a (Table 4, entry 10) was treated with [hmim]Br using various mild bases like aq. NaHCO\(_3\), KHCO\(_3\) etc. under MW and gratifyingly the [hmim]Br–aq. NaHCO\(_3\) (20 mol%) combination was found to provide 10b in an improved 67% yield. Thereafter, this protocol was applied on various other cinnamic acids (Table 4). Significantly, it provided an improved decarboxylative access towards industrially important hydroxy styrenes including 4-vinyl guaiacol (Table 4, entry 11), a FEMA GRAS (Flavor and Extract Manufacturer’s Association; Generally Regarded As Safe) approved flavoring agent [Sinha \textit{et al.} (2007)]. It would also be evident from Table 4 that an ortho or para hydroxy substitution at aromatic ring provided a comparatively favorable condition for decarboxylation as compared to 3-hydroxy counterpart (Table 4, entry 20). The foregoing result is presumably due to the well known resonance stabilization provided by the ortho/para quinomethide [Nomura \textit{et al.} (2005); Sinha \textit{et al.} (2007)].

The above success with 4 or 2-hydroxy substituted cinnamic acids motivated us to explore the hitherto unrealized metal/quinoline free decarboxylation of methoxylated cinnamic acids like 15a (Table 4, entry 15) with no 4 or 2-hydroxy substitution. However, no product (15b) could be detected when 15a was treated with a combination of [hmim]Br and aq.
Table 4. Decarboxylation of cinnamic acid derivatives using [hmim]Br-base under microwave irradiation.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate (a)</th>
<th>Reaction time (min)</th>
<th>Product (b)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>MeO-OCOH</td>
<td>4</td>
<td>MeO-CH=CH</td>
<td>67</td>
</tr>
<tr>
<td>11</td>
<td>HO-OCOH</td>
<td>4</td>
<td>HO-CH=CH</td>
<td>69</td>
</tr>
<tr>
<td>12</td>
<td>HO-OCOH</td>
<td>4</td>
<td>HO-CH=CH</td>
<td>50</td>
</tr>
<tr>
<td>13</td>
<td>HO-OCOH</td>
<td>4</td>
<td>HO-CH=CH</td>
<td>60</td>
</tr>
<tr>
<td>14</td>
<td>HO-OCOH</td>
<td>7</td>
<td>HO-CH=CH</td>
<td>64</td>
</tr>
<tr>
<td>15</td>
<td>HO-OCOH</td>
<td>20</td>
<td>15b'</td>
<td>19 +5c</td>
</tr>
<tr>
<td>16</td>
<td>HO-OCOH</td>
<td>20</td>
<td>16b'</td>
<td>5c +19</td>
</tr>
<tr>
<td>17</td>
<td>HO-OCOH</td>
<td>20</td>
<td>17b'</td>
<td>5c +6c</td>
</tr>
<tr>
<td>18</td>
<td>11a</td>
<td>4</td>
<td>14b</td>
<td>50d</td>
</tr>
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<td>19</td>
<td>14b</td>
<td>20</td>
<td>14b</td>
<td>27e</td>
</tr>
<tr>
<td>20</td>
<td>16b</td>
<td>30</td>
<td>16b</td>
<td>6d</td>
</tr>
<tr>
<td>21</td>
<td>17b</td>
<td>30</td>
<td>17b</td>
<td>3c</td>
</tr>
</tbody>
</table>

*a*CEM Discover microwave. *b* Yield of pure isolated product. General condition: substrate (entries 10-14, 18-19) (1.5 mmol), [hmim]Br (1.5 ml), water (8 mmol), NaHCO₃ (20 mol%) under microwave for 4-30 min (150W, 140°C), in case of entries 15-17 and 20-21: DBU (1.5 mmol) was used in place of NaHCO₃ while rest of the conditions were same. *c* Based on GC-MS analysis. *d* After the formation of styrene (11b) in 4 min (MW) as described in general condition above, dimethyl sulphate (2 mmol), water (5 ml), sodium hydroxide (2 mmol) were added to the same pot and the mixture stirred at ice bath for 30 min to obtain 17b. *e* NaOH (1.5 mmol) was used instead of NaHCO₃. Published in Adv. Synth. Catal. 2008, 350, 2910-2910.

NaHCO₃ under microwave irradiation even after 60 min of MW while the starting material remained unreacted. Similarly, the replacement of NaHCO₃ with stronger bases like methylimidazole, piperidine etc. also proved futile for improving the reaction performance.
Consequently the use of a hindered base like DBU \((pK_a = 12)\) was envisaged as it has been reported for an efficient albeit metal catalyzed decarboxylation of unsaturated fatty acids [Hori et al. (1981)]. Surprisingly, the treatment of 15a with a combination of [hmim]Br-DBU under microwave irradiation for 20 min provided the first metal-free decarboxylation of methoxylated cinnamic acid (Table 4, entry 15). The above result was especially interesting as a subsequent literature search revealed that DBU in the absence of ionic liquid had earlier proved to be ineffective for promoting decarboxylation of similar methoxylated substrates under microwave conditions [Bernini et al. (2007)]. In this context, it appears plausible that it is the unique combination of ionic liquid with DBU that provides an effective system for promoting decarboxylation of 15a even in the absence of a metal catalyst. Moreover, 15a also underwent a novel simultaneous decarboxylation and demethylation to give an unexpected side product 2-hydroxy-4-methoxy styrene (15b', 5% yield). It would be apparent from Table 4, the above [hmim]Br-DBU system was also found to be applicable for decarboxylation of other methoxylated cinnamic acids 16-17a (Table 4) into methoxy styrenes (16b-17b). Interestingly, 16a underwent a concurrent demethylation to give 2-hydroxy-3-methoxy styrene (16b') as the major product. In order to further increase the yield of methoxylated styrene 17b, it was planned to develop a one pot decarboxylation-methylation of corresponding hydroxy cinnamic acid. Thus, 4-hydroxy-3-methoxy cinnamic acid 11a upon decarboxylation with [hmim]Br-aq. NaHCO\(_3\) protocol provided corresponding styrene 11b (as revealed by comparison with standard on TLC). Thereafter, the obtained 11b was methylated by addition of dimethyl sulfate (2 mmol), water (5 ml), sodium hydroxide (2 mmol) in the same pot and reaction mixture stirred in ice bath for 30 min to provide the corresponding 3,4-dimethoxy styrene 17b (Table 4, entry 18) in 50% yield. On the other hand, coumarin 19a (Table 4) also provided the corresponding styrene 14b through a simultaneous hydrolysis-decarboxylation (Table 4, entry 19). However, the above reaction required prior addition of a few drops of sodium hydroxide (1.5 mmol) to [hmim]Br for initial hydrolysis of lactone ring to be followed by subsequent decarboxylation of resulting cinnamic acid.

After the above success with hydroxycinnamic acids (Table 4, entries 10-21), it was planned to apply the ionic liquid based strategy for decarboxylation of hydroxy substituted \(\alpha\)-phenylcinnamic acids into biologically important hydroxystilbenes [Baur and Sinclair
Ionic Liquid assisted ...... Chapter 2

(2006); Likhtenshtein (2009)]. Hence, α-phenyl-4-hydroxycinnamic acid 22a was treated with [hmim]Br under MW irradiation (30 min), wherein, the corresponding stilbene was obtained in 84% yield. However, when above method using neat [hmim]Br or even its combination with NaHCO$_3$ or DBU was applied on various other α–phenylcinnamic acids like α -phenyl-4-hydroxy-3-methoxycinnamic acid (23a) or α -phenyl-4,4’-dihydroxy-3-methoxycinnamic acid (24a), the corresponding stilbenes 23b-24b were obtained in comparatively lower yield (upto 41%) after 45 min of MW irradiation. Consequently, various other ionic liquids from Table 1 were screened and neat ionic liquid [Hmim]PTSA was surprisingly found to be effective for decarboxylation of 23a (Table 5, 72% yield), while 22b was obtained in 86% yield (Table 5, entry 22). Similarly, the other α-phenyl-4-

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate (a)</th>
<th>Reaction time (min)</th>
<th>Product (b)</th>
<th>Yield$^b$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>22</td>
<td>HO C$_6$H$_5$COOH</td>
<td>60</td>
<td>HO C$_6$H$_5$</td>
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<td>23</td>
<td>MeO C$_6$H$_5$COOH</td>
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<td>MeO C$_6$H$_5$</td>
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<tr>
<td>24</td>
<td>HO C$_6$H$_4$(4-OH)COOH</td>
<td>90</td>
<td>HO C$_6$H$_4$(4-OH)</td>
<td>65</td>
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<tr>
<td>25</td>
<td>HO C$_6$H$_4$(3-OMe)COOH</td>
<td>90</td>
<td>HO C$_6$H$_4$(3-OMe)</td>
<td>70</td>
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<tr>
<td>26</td>
<td>MeO C$_6$H$_4$(4-OMe)COOH</td>
<td>90</td>
<td>MeO C$_6$H$_4$(4-OMe)</td>
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<td>MeO C$_6$H$_5$COOH</td>
<td>80</td>
<td>MeO C$_6$H$_5$</td>
<td>67</td>
</tr>
</tbody>
</table>

hydroxycinnamic acids (Table 5, entries 24-26) also underwent decarboxylation into
corresponding stilbenes (upto 79% yield) without the addition of any catalyst. Moreover,
the above conditions were also conducive for a useful one pot two step deacetylation-
decarboxylation of acetylated α-phenylcinnamic acids (Table 5, entries 27-28).

With an ionic liquid based decarboxylation platform for synthesis of indoles, styrenes and
stilbenes (Tables 2-5) in hand, it was planned to extend the methodology towards aromatic
acids which are known to be immensely useful synthons [Baudoin (2007); Myers et al.
(2002)]. It is pertinent to mention that decarboxylation of aromatic acids has been widely
recognized to be one of the most challenging transformations which requires either an
indispensable use of transition metals [Dickstein et al. (2007); Myers et al. (2002)] or
specialized reaction conditions involving Pd-supercritical water [Matsubara et al. (2004)]
etc. Thus, it was initially planned to explore a neat ionic liquid assisted metal-free
decarboxylation of 3,5-dichloro-4-hydroxy benzoic acid (29a) into 2,6-dichlorophenol, a
pharmaceutically important phenol [Mukhopadhyay and Chandalia (1999)]. In this context,
a survey of reaction temperature revealed that treatment of 29a with [hmim]Br/water at
190°C under 25 min of MW (200W) was effective to provide corresponding phenol 29b in
31% yield. Similarly, the above protocol was beneficial for efficient decarboxylation of
ortho/para nitro substituted phenyl acetic acids 30b-31b into synthetically useful alkyl nitro
benzenes (85 and 78% yield respectively) [Bull et al. (1996)] without addition of any
catalyst. On the other hand, a low yield (23%) was obtained in case of 2-chloro-4-
nitrobenzoic acid 32a (32b). In the course of further efforts for improving the reaction
performance, the role of a combination of [hmim]Br with aq. NaHCO₃ was evaluated.
Hence, 29a was treated with [hmim]Br and NaHCO₃ (20 mol%) and gratifyingly 29b was
obtained in an improved 61% yield (Table 6, entry 29). Similarly, the above [hmim]Br-
aq.NaHCO₃ reagent system also enhanced the reaction performance of 30a and 31a as the
corresponding decarboxylated products were obtained in comparatively shorter reaction
times as compared to the case with neat [hmim]Br (Table 6, entries 30-31). In addition, the
treatment of nitro substituted carboxylic acid (32a) (Table 6, entry 32) under above reaction
conditions also furnished the corresponding 32b in an improved 55% yield. It is worthwhile
to mention that above approach provides a useful addition as such substrates have recently
been much explored for decarboxylative couplings [Gooßen et al. (2006); Gooßen et al.
Curiously, the 4-nitrobenzoic acid (Table 6, entry 33) underwent decarboxylation in longer reaction time of 45 min with 15% yield along with formation of some esterified side products. Similarly, other nitro substituted benzoic acid (Table 6, entries 34-35) didn’t undergo efficient decarboxylation. Interestingly, diphenyl acetic acid underwent facile decarboxylation (Table 6, entry 37), however, no product formation was detected in the

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate (a)</th>
<th>Reaction time (min)</th>
<th>Product (b)</th>
<th>Yield (%)</th>
</tr>
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<tbody>
<tr>
<td>29</td>
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<td>20</td>
<td>ClClO2O2</td>
<td>61</td>
</tr>
<tr>
<td>30</td>
<td>O2N</td>
<td>5</td>
<td>O2N</td>
<td>92</td>
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<td>31</td>
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</tr>
<tr>
<td>32</td>
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<td>20</td>
<td>O2N</td>
<td>55</td>
</tr>
<tr>
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<td>45</td>
<td>O2NCl</td>
<td>15&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>34</td>
<td>O2N</td>
<td>45</td>
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<td>24&lt;sup&gt;c&lt;/sup&gt;</td>
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<tr>
<td>35</td>
<td>O2N</td>
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<td>O2N</td>
<td>nd&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
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<td>Cl</td>
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<tr>
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</tr>
<tr>
<td>39</td>
<td>MeO</td>
<td>45</td>
<td>MeO</td>
<td>nd&lt;sup&gt;c-d&lt;/sup&gt;</td>
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<tr>
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<td>45</td>
<td>MeO</td>
<td>nd&lt;sup&gt;c-d&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> CEM Discover monomode microwave. <sup>b</sup> Yield of pure isolated product. <sup>c</sup> based on GC-MS analysis. <sup>d</sup> Not detected General condition: substrate (entries 29-40) (2.1 mmol), [hmim] Br (1.5 ml), water (8 mmol), NaHCO<sub>3</sub> (20 mol %) under microwave for 5-60 min (200 W, 190°C).

case of biphenyl-4-carboxylic acid, 4-methoxy benzoic acid or thiophene-2-carboxylic acid (Table 6, entries 38-40). On the other hand, the developed methodology was found to be amenable towards decarboxylation of diverse 4-hydroxy benzoic acids (Table 7, entries 41-45) into industrially important flavoring agents like syringol, guaiacol [Crouzet et al. (1997)] and anti-oxidant catechol [Cao et al. (2008)]. Thus, it would be apparent from Table 6-7 that the presence of a 4-hydroxy or 2-chloro/4-nitro substitution at the aromatic ring is necessary for a metal-free decarboxylation to proceed under above conditions.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate (a)</th>
<th>Reaction time (min)</th>
<th>Product (b)</th>
<th>Yield (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
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<tr>
<td>41</td>
<td>R'=H, CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>15</td>
<td></td>
<td>50</td>
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<tr>
<td>42</td>
<td>R=COOH, CH&lt;sub&gt;2&lt;/sub&gt;COOH etc.</td>
<td>15</td>
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<tr>
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<td>R=COOH, CH&lt;sub&gt;2&lt;/sub&gt;COOH etc.</td>
<td>15</td>
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<td>54</td>
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<tr>
<td>44</td>
<td>R=COOH, CH&lt;sub&gt;2&lt;/sub&gt;COOH etc.</td>
<td>15</td>
<td></td>
<td>31</td>
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<tr>
<td>45</td>
<td>R=COOH, CH&lt;sub&gt;2&lt;/sub&gt;COOH etc.</td>
<td>15</td>
<td></td>
<td>10&lt;sup&gt;c&lt;/sup&gt;</td>
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</tbody>
</table>

<sup>a</sup> CEM Discover monomode microwave. <sup>b</sup> Yield of pure isolated product. <sup>c</sup> based on GC-MS analysis. <sup>d</sup> Not detected. General condition: substrate (entries 41-45) (2.1 mmol), [hmim] Br (1.5 ml), water (8 mmol), NaHCO<sub>3</sub> (20 mol %) under microwave for 15 min (200W, 190°C).

After examining the substrate scope of developed ionic liquid based metal-free decarboxylation strategy, it was interesting to evaluate its mechanistic implications. In particular, the unprecedented decarboxylation of various indole and aromatic acid derivatives under catalyst free conditions using neat ionic liquid appeared noteworthy. Similarly, though the decarboxylation of hydroxy cinnamic acid derivatives and nitro benzene derivatives appears to be facilitated in part by the peculiar resonance stabilization
in these systems [Gooßen et al. (2006); Sinha et al. (2007)], however, the above stabilization has also been usually reported following an initial base/acid catalyzed step. In this context, a general mechanistic pathway (Figure 2) for neat ionic liquid catalyzed decarboxylation plausibly involves an initial ionic liquid promoted formation of carboxylate anion which is facilitated in part by the enhanced dissociation constants of aryl acids in presence of ionic liquids. Subsequently, the ionic liquid facilitates efficient absorption of microwave energy to provide the decarboxylated product.

**Figure 2**

### 2.6 Conclusion

In summary, ionic liquids have been found to be efficient catalysts cum solvents for metal and quinoline free decarboxylation of diverse N-heteroaryl and aryl carboxylic acids under microwave irradiation in aqueous condition. The methodology showed wide substrate scope towards synthesis of pharmacologically and industrially important aromatic compounds including indoles, styrenes, stilbenes, nitro or hydroxy arene derivatives. In the case of indole carboxylic acids and α-phenylcinnamic acids, decarboxylation proceeded well in neat [hmim]Br and [Hmim]PTSA respectively. On the other hand, addition of a mild base like aq. NaHCO₃ to [hmim]Br was found to improve the decarboxylation of cinnamic and aromatic acid substrates. The developed methodology offers several inherent
advantages like reduction in waste and hazards, recyclability of reagent system, short reaction times besides ease of product recovery.

2.7 Experimental Section

2.7.1 General Procedure
The starting materials were reagent grade (purchased from Merck and Sigma Aldrich) except α-phenylcinnamic acid derivatives which were prepared through previously reported Perkin reaction of respective benaldehydes [Sinha et al. (2007)] and fully characterized by 1H and 13C NMR. The ionic liquids were purchased (Merck and Acros) or synthesized using an earlier reported procedure [Nockemann et al. (2005)]. The purity of ionic liquids was checked by 1H NMR before their use. The solvents used for isolation/purification of compounds were obtained from commercial sources (Merck) and used without further purification. 1H (300 MHz) and 13C (75.4 MHz) NMR spectra were recorded on a Bruker Avance-300 spectrometer. GC-MS analysis was undertaken using a Shimadzu-2010 spectrometer. CEM Discover® focused microwave (2450 MHz, 300W) was used wherever mentioned. The temperature of reactions in microwave experiments was measured by an inbuilt infrared temperature probe that determined the temperature on the surface of reaction flask. The sensor is attached in a feedback loop with an on-board microprocessor to control the temperature rise rate. In the case of conventional heating in oil bath, the temperature of reaction mixture was monitored by an inner thermometer.

2.7.2 Optimization of reaction conditions

2.7.2.1 Decarboxylation of N-heteroaryl carboxylic acids

2.7.2.1.1 Decarboxylation of indole-2-carboxylic acid (1a) using [bmim]OH (Table 1, entry 1)
A mixture of indole-2-carboxylic acid (0.2 g, 1.2 mmol) and [bmim]OH (1.5 ml) was irradiated under focused microwave system in parts (250W, 240°C) for 15 min. After the completion of reaction (on TLC basis), the reaction mixture was cooled and extracted with ethyl acetate (3x10 ml) and the ionic liquid left as residue. The combined organic layer was washed with brine, dried (anhyd. Na2SO4) and vacuum evaporated to obtain a crude
product which was purified on silica-gel (60-120 mesh size) column with a 1:10 mixture of ethylacetate and hexane to provide 1b (0.087g, 60% yield).

**Indole (Table 1, entry 1)**

![Indole molecule](image)

White solid, m. p. 51-53°C (lit. m. p. 52–54°C) [Jones and Chapman (1993)], \(^1\)H NMR \(\delta\) (CDCl\(_3\), 300 MHz) 7.93 (1H, s), 7.70 (1H, d, \(J=7.67\) Hz), 7.35 (1H, d, \(J=8.07\) Hz), 7.25-7.11 (3H, m), 6.57 (1H, s); \(^{13}\)C NMR \(\delta\) (CDCl\(_3\), 75.4 MHz) 135.8, 127.9, 124.3, 122.0, 120.8, 119.9, 111.2 and 102.6.

### 2.7.2.1.2 Decarboxylation of 1a using various other ionic liquids [Hmim]PTSA, [bmim]PF\(_6\), [bmim]BF\(_4\), [bmim]Cl, [bmim]Br, [hmim]Br) (Table 1, entries 2-7)

Indole-2-carboxylic acid (0.2 g, 1.2 mmol) was treated separately with the following ionic liquids (1.5 ml each); [Hmim]PTSA, [bmim]PF\(_6\), [bmim]BF\(_4\), [bmim]Cl, [bmim]Br, [hmim]Br under the microwave conditions mentioned in preceding section. After the completion of reaction, each of the reaction mixture was worked up as mentioned in the preceding section. The column purification (Silica-gel (60-120 mesh size)) of crude mixture of a majority of above reactions with a 1:10 mixture of ethylacetate and hexane provided the desired 1b in traces to 79% yield. However, an enhanced yield (88%) of 1b was obtained in the case when [hmim]Br was used.

### 2.7.2.1.3 Optimized procedure for decarboxylation of 1a using combination of [hmim]Br-H\(_2\)O (Table 1, entry 9)

A mixture of indole-2-carboxylic acid (1.2 mmol), [hmim]Br (1.5 ml) and water (8 mmol) was irradiated under focused microwave system in parts (250W, 240°C) for 15 min. After the completion of reaction, the reaction mixture was worked up and purified as mentioned in section 2.7.2.1.1 to provide the desired 1b (0.127g, 88% yield) whose NMR (\(^1\)H and \(^{13}\)C) spectrum matched well with that obtained in section 2.7.2.1.1.

The above procedure was also followed for decarboxylation of various other heteroaromatic acids (Table 2, entries 2-6; Table 3, entries 7-9).
5-Chloro-indole 2b (2b, Table 2)

![Structure](image)

White solid, m. p. 70-73°C (lit. m. p. 70–72°C) [Gu et al. (2007)], \(^1\)H NMR \(\delta\) (CDCl\(_3\), 300 MHz) 8.11 (1H, s), 7.56 (1H, s), 7.25 (1H, d, \(J=8.51\) Hz), 7.16-7.08 (2H, m), 6.44 (1H, s); \(^{13}\)C NMR \(\delta\) (CDCl\(_3\), 75.4 MHz) 134.1, 128.9, 125.4, 122.3, 120.1, 112.0 and 102.4.

Indazole (3b, Table 2)

![Structure](image)

White solid, m. p. 146-148°C (lit. m. p 147–149°C) [Lukin et al. (2006)], \(^1\)H NMR \(\delta\) (CD\(_3\)COCD\(_3\), 300 MHz) 12.25 (1H, s), 7.99 (1H, s), 7.72 (1H, d, \(J=7.67\) Hz), 7.53 (1H, d, \(J=8.07\) Hz), 7.31 (1H, t, \(J=7.67\) Hz), 7.08 (1H, t, \(J=7.67\) Hz); \(^{13}\)C NMR \(\delta\) (CD\(_3\)COCD\(_3\), 75.4 MHz) 140.4, 133.7, 126.0, 123.4, 120.5, 120.3 and 109.9.

Quinoline (4b, Table 2)

![Structure](image)

Light yellow liquid [Reddy and Ganesh (2000)], \(^1\)H NMR \(\delta\) (CDCl\(_3\), 300 MHz) 8.76 (1H, s), 8.01 (1H, d, \(J=8.88\) Hz), 7.95 (1H, d, \(J=8.48\) Hz), 7.63 (1H, d, \(J=8.48\) Hz), 7.57 (1H, t, \(J=7.27\) Hz), 7.38 (1H, t, \(J=7.67\) Hz), 7.21-7.16 (1H, m); \(^{13}\)C NMR \(\delta\) (CDCl\(_3\), 75.4 MHz) 149.9, 148.2, 136.0, 129.3, 128.2, 127.7, 126.5 and 121.0.

1-Methylindole (6b, Table 2)

![Structure](image)

Light yellow liquid [Gu et al. (2007)], \(^1\)H NMR \(\delta\) (CDCl\(_3\), 300 MHz) 7.74 (1H, d, \(J=7.87\) Hz), 7.42 (1H, d, \(J=8.23\) Hz), 7.34-7.28 (1H, m), 7.22-7.17 (1H, m), 7.12 (1H, d, \(J=3.11\) Hz); 6.58 (1H, d, \(J=3.11\) Hz); 3.84 (3H, s); \(^{13}\)C NMR \(\delta\) (CDCl\(_3\), 75.4 MHz) 137.1, 129.2, 128.9, 121.9, 121.3, 119.7, 109.6, 101.3 and 32.8.
3-Methylindole (7b, Table 3)

White solid, m. p. 94-97°C (lit. m. p. 93–95°C) [Jensen et al. (1995)], $^1$H NMR $\delta$ (CDCl$_3$, 300 MHz) 7.74 (1H, s), 7.59 (1H, d, $J$=7.27 Hz), 7.31 (1H, d, $J$=7.27 Hz), 7.21-7.09 (2H, m), 6.91 (1H, s), 2.33 (3H, s); $^{13}$C NMR $\delta$ (CDCl$_3$, 75.4 MHz) 136.3, 128.3, 121.9, 121.6, 119.1, 118.9, 111.7, 111.0 and 9.7.

1,3-Dimethylindole (8b, Table 3)

Colorless liquid [Jefford et al. (1984)], $^1$H NMR $\delta$ (CDCl$_3$, 300 MHz) 7.60 (1H, d, $J$=8.07 Hz), 7.30-7.24 (2H, m), 7.16-7.10 (1H, m), 6.81 (1H, s), 3.71 (3H, s), 2.35 (3H, s); $^{13}$C NMR $\delta$ (CDCl$_3$, 75.4 MHz) 137.0, 128.7, 126.6, 120.5, 119.0, 118.5, 110.1, 109.0, 32.5 and 9.6.

2,3-Dimethylindole (9b, Table 3)

Colorless viscous liquid [An et al. (1997)], $^1$H NMR $\delta$ (CDCl$_3$, 300 MHz) 7.52 (1H, d, $J$=6.46 Hz), 7.23 (1H, d, $J$=1.86 Hz), 7.15-7.10 (2H, m), 2.32 (3H, s), 2.25 (3H, s); $^{13}$C NMR $\delta$ (CDCl$_3$, 75.4 MHz) 135.0, 130.74, 129.35, 120.78, 118.94, 117.87, 110.15, 106.80, 11.15 and 8.34.

2.7.2.2 Optimization of conditions for decarboxylation of cinnamic acids

2.7.2.2.1 Decarboxylation of 4-hydroxy-3,5-dimethoxy cinnamic acid (10a) using combination of [hmim]Br and water

A mixture of 4-Hydroxy-3,5-dimethoxy cinnamic acid (10a, 0.34 g, 1.5 mmol), [hmim]Br (1.5ml) and water (8 mmol) was irradiated under focused microwave system in parts
(150W, 140 °C) for 4 min. The reaction mixture was worked up and purified as mentioned in section 2.7.2.1.1 and 10b was obtained in 34% yield (0.09 g).

**4-Hydroxy-3,5-dimethoxy styrene (10b, Table 4)**

![4-Hydroxy-3,5-dimethoxy styrene](image)

Colorless liquid [Nomura et al. (2005)]. $^1$H NMR δ (CDCl$_3$, 300 MHz) 6.58 (2H, s), 6.55-6.50 (1H, m), 5.56 (1H, d, $J$=17.76 Hz), 5.09 (1H, d, $J$=10.90 Hz), 3.83 (6H, s); $^{13}$C NMR δ (CDCl$_3$, 75.4 MHz) 147.1, 136.8, 134.8, 129.2, 111.8, 103.0 and 56.2.

**2.7.2.2 Decarboxylation of 10a using combination of [hmim]Br/H$_2$O and various inorganic bases**

The reaction was performed in the same manner as described in section 2.7.2.2.1, however, various bases like NaOAc, KHCO$_3$, K$_2$CO$_3$ each were explored in combination with [hmim]Br and water. Each of the above reactions upon completion and work up as mentioned in section 2.7.2.1.1 led to a lower yield of 10b.

**2.7.2.2.3 Final optimized procedure for decarboxylation of 10a using combination of [hmim]Br/water and NaHCO$_3$ (Table 4, entry 10)**

A mixture of 4-hydroxy-3,5-dimethoxy cinnamic acid (10a, 0.34 g, 1.5 mmol), [hmim]Br (1.5ml), water (8 mmol) and 20 mol% NaHCO$_3$ (0.42 mmol) was irradiated under focused microwave system in parts (150W, 140 °C) for 4 min. The reaction mixture was worked up and purified as mentioned in section 2.7.2.2.1 and 10b was obtained in an optimum 67% yield (0.18 g). The spectral data ($^1$H and $^{13}$C NMR) of above 10b matched well with that obtained in section 2.7.2.2.1.

The above procedure was also followed for decarboxylation of various other cinnamic acids (Table 4, entries 11-14, 18-19). However, in the case of entries 15-17 and 20-21 (Table 4), DBU (1.5 mmol) was used in place of NaHCO$_3$ while rest of the conditions were the same as in section 2.7.2.2.3.
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4-Hydroxy-3-methoxy styrene (11b, Table 4)

Colorless viscous liquid [Nomura et al. (2005)], $^1$H NMR $\delta$ (CDCl$_3$, 300 MHz) 6.88-6.81 (3H, m), 6.63-6.54 (1H, m), 5.68 (1H, s), 5.71 (1H, d, $J$=17.56 Hz), 5.09 (1H, d, $J$=10.92 Hz), 3.84 (3H, s); $^{13}$C NMR $\delta$ (CDCl$_3$, 75.4 MHz) 146.6, 145.6, 136.6, 103.3, 120.1, 114.4, 111.4, 108.1 and 55.9.

3,4-Dihydroxy styrene (12b, Table 4)

Colorless viscous liquid [Nomura et al. (2005)], $^1$H NMR $\delta$ (CDCl$_3$, 300 MHz) 6.95 (1H, d, $J$=7.16 Hz), 6.69 (1H, d, $J$=7.16 Hz), 6.67 (1H, s), 6.61-6.39 (1H, m), 5.63 (1H, d, $J$=16.8 Hz), 5.29 (1H, d, $J$=11.2 Hz); $^{13}$C NMR $\delta$ (CDCl$_3$, 75.4 MHz) 144.4, 143.6, 136.2, 128.9, 121.1, 118.9, 114.3 and 112.1.

4-Hydroxy styrene (13b, Table 4)

Colorless liquid [Nomura et al. (2005)], $^1$H NMR $\delta$ (CDCl$_3$, 300 MHz) 7.25 (2H, d, $J$=8.07 Hz), 6.75 (2H, d, $J$=8.87 Hz), 6.63-6.54 (1H, m), 5.56 (1H, d, $J$=17.36 Hz), 5.52 (1H, s), 5.07 (1H, d, $J$=10.50 Hz); $^{13}$C NMR $\delta$ (CDCl$_3$, 75.4 MHz) 155.4, 136.2, 130.6, 127.6, 115.4 and 111.6.

2-Hydroxy styrene (14b, Table 4)

Colorless oil [Nomura et al. (2005)], $^1$H NMR $\delta$ (CDCl$_3$, 300 MHz) 7.38 (1H, d, $J$=7.67 Hz), 7.15-7.07 (1H, m), 6.99-6.91 (1H, m), 6.89-6.86 (1H, m), 6.76 (1H, d, $J$=8.48 Hz), 5.74 (1H, d, $J$=17.67 Hz), 5.33 (1H, d, $J$=11.30 Hz); $^{13}$C NMR $\delta$ (CDCl$_3$, 75.4 MHz) 152.9, 131.5, 128.9, 127.3, 125.0, 120.9, 115.9 and 115.6.
**Chapter 2**

2.4-Dimethoxy styrene (15b, Table 4)

![Chemical structure of 2,4-Dimethoxy styrene](image)

Colorless liquid [Shin *et al.* (2001)], $^1$H NMR $\delta$ (CDCl$_3$, 300 MHz), 7.42 (1H, d, $J$=8.23 Hz), 7.01-6.92 (1H, m), 6.51-6.45 (2H, m), 5.67 (1H, d, $J$=17.75 Hz), 5.18 (1H, d, $J$=11.16 Hz), 3.85 (3H, s), 3.83 (3H, s); $^{13}$C NMR $\delta$ (CDCl$_3$ 75.4 MHz) 160.9, 158.2, 131.6, 127.6, 120.3, 112.6, 105.1, 98.8 and 55.7.

2-Hydroxy-3-methoxy styrene (16b', Table 4)

![Chemical structure of 2-Hydroxy-3-methoxy styrene](image)

Colorless liquid [Ingemarsson (1998)], $^1$H NMR $\delta$ (CDCl$_3$, 300 MHz) 7.11 (1H, d, $J$=1.83 Hz), 7.08-6.99 (1H, m), 6.86 -6.77 (2H, m), 5.91 (1H, s), 5.86 (1H, d, $J$=17.56 Hz), 5.35 (1H, d, $J$=11.34 Hz), 3.91 (3H, s); $^{13}$C NMR $\delta$ (CDCl$_3$ 75.4 MHz) 147.0, 143.7, 131.6, 124.3, 119.7, 119.2, 115.2, 110.0 and 56.5.

### 2.7.2.3 Optimization of conditions for decarboxylation of $\alpha$-phenylcinnamic acids

#### 2.7.2.3.1 Decarboxylation of $\alpha$-phenyl-4-hydroxy-3-methoxycinnamic acid (23a) using [hmim]Br/water alone or its combination with various bases (23a was taken in place of 22a as the decarboxylation of former proved difficult using [hmim]Br/base)

A mixture of $\alpha$-phenyl-4-hydroxy-3-methoxycinnamic acid (23a, 0.23 g, 0.83 mmol), [hmim]Br (1.5 ml) and water (8 mmol) was irradiated under focused microwave system in parts (200W, 190°C) for 45 min. The reaction mixture was worked up and purified as mentioned in section 2.7.2.1.1 and 23b was obtained in only 20% yield. Subsequently, the above reaction was also conducted using other bases like NaHCO$_3$ or DBU, however, the yield of 23b was found to increase upto 41% only.

4-Hydroxy-3-methoxy stilbene (23b)

![Chemical structure of 4-Hydroxy-3-methoxy stilbene](image)
White solid, m. p. 130-132 °C (lit. m. p 132-134°C) [Sinha et al. (2007)], $^1$H NMR $\delta$ (CDCl$_3$, 300 MHz) 7.45 (2H, d, $J=7.41$ Hz), 7.32-7.27 (2H, m), 7.21-7.16 (1H, m), 7.02-6.85 (5H, m), 5.66(1H, s), 3.89(3H, s); $^{13}$C NMR $\delta$ (CDCl$_3$, 75.4MHz). 146.7, 145.6, 137.6, 130.0, 128.7, 127.2, 126.5, 126.2, 120.5, 114.6, 108.3 and 55.9.

2.7.2.3.2 Optimized procedure for decarboxylation of $\alpha$-phenyl-4-hydroxy-3-methoxycinnamic acid (23a) using [Hmim]PTSA (Table 5, entry 23)  
A mixture of 23a (0.23 g, 0.83 mmol), [Hmim]PTSA (2 g) and water (8 mmol) was irradiated under focused microwave system in parts (200W, 190°C) for 90 min. The reaction mixture was worked up and purified as mentioned in section 2.7.2.1.1 and 23b was obtained in an optimum 72% yield (0.18 g). The spectral data ($^1$H and $^{13}$C NMR) of above obtained 23b matched well with that obtained in section 2.7.2.3.1.

The above procedure was also followed for decarboxylation of various other $\alpha$-phenyl cinnamic acids (Table 5, entries 22, 24-28).

4-Hydroxy stilbene; (22b,Table 5)

White solid, m. p. 184-186 °C (lit. m. p 185-187°C) [Sinha et al. (2007)], $^1$H NMR $\delta$ (MeOD, 300 MHz) 7.40 (2H, d, $J=7.68$ Hz), 7.31 (2H, d, $J=8.51$ Hz), 7.24-7.19 (2H, m), 7.12-7.08 (1H, m), 7.02 (1H, d, $J=16.74$ Hz), 6.90 (1H, d, $J=16.74$ Hz), 6.72 (2H, d, $J=8.51$ Hz); $^{13}$C NMR $\delta$ (MeOD 75.4 MHz) 157.0, 137.9, 129.1, 128.2, 128.1, 127.5, 126.6, 125.8, 125.4 and 115.1.

4,4'-Dihydroxy-3-methoxy stilbene; (24b, Table 5)

Brown solid; (m. p. 210-214°C) [Kumar et al. (2007)], $^1$H NMR $\delta$ (CD$_3$COCD$_3$, 300 MHz)
8.36 (1H, s), 7.61 (1H, s), 7.33 (2H, d, J=9.3 Hz), 7.12 (1H, s), 6.97-6.92 (3H, m), 6.77-6.72 (3H, m), 3.81 (3H, s); $^{13}$C NMR δ (CD$_3$COCD$_3$, 75.4 MHz) 156.8, 147.6, 146.2, 130.0, 129.5, 127.4, 125.9, 125.7, 119.8, 115.5, 115.0, 108.9 and 55.3.

4-Hydroxy-3′-methoxy stilbene (25b, Table 5)

![Chemical structure of 4-Hydroxy-3′-methoxy stilbene](image)

White solid m. p. 133–135°C (lit. m. p 131–134°C) [Sinha et al. (2007)], $^1$H NMR δ (CD$_3$COCD$_3$, 300 MHz) 8.46 (1H, s), 7.39 (2H, d, J=8.51 Hz), 7.20–7.13 (1H, m), 7.07–7.04 (3H, m), 6.97 (1H, d, J=16.14 Hz), 6.80 (2H, d, J=8.51 Hz), 6.74 (1H, d, J=7.14 Hz), 3.74 (3H, s); $^{13}$C NMR δ (CD$_3$COCD$_3$, 75.4 MHz) 160.1, 157.4, 139.4, 129.5, 129.0, 128.7, 127.9, 125.5, 118.7, 115.5, 112.7, 111.3 and 54.6.

4-Hydroxy-3,4′-dimethoxy stilbene (26b, Table 5)

![Chemical structure of 4-Hydroxy-3,4′-dimethoxy stilbene](image)

White solid, m. p. 164-167°C (lit. m. p 163–166°C) [Sinha et al. (2007)], $^1$H NMR δ (CDCl$_3$, 300 MHz) 7.37 (2H, d, J=8.48 Hz), 6.95-6.92 (2H, m), 6.84-6.81 (5H, m), 3.88 (3H, s), 3.76 (3H, s); $^{13}$C NMR δ (CDCl$_3$, 75.4 MHz) 159.0, 146.7, 145.2, 130.3, 127.4, 126.6, 126.1, 120.1, 114.5, 114.1, 108.0, 55.9 and 55.3.

### 2.7.2.4 Optimization of conditions for decarboxylation of aromatic acid derivatives

#### 2.7.2.4.1 Decarboxylation of 3,5-dichloro-4-hydroxy benzoic acid (29a) using [hmim]Br/water

A mixture of 3,5-dichloro-4-hydroxy benzoic acid (29a, 0.43g, 2.1 mmol), [hmim]Br (1.5 ml) and water (8 mmol) was irradiated under focused microwave system in parts (200W, 190°C) for 25 min. The reaction mixture was worked up and purified as mentioned in section 2.7.2.1.1 and 29b was obtained in 31% yield.

**2,6-Dichlorophenol (29b)**

![Chemical structure of 2,6-Dichlorophenol](image)
White solid, m. p. 67-70°C (lit. m. p 68-69°C) [Mukhopadhyay and Chandalia (1999)], ^1^H NMR δ (CDCl₃, 300 MHz) 7.29 (2H, d, J=8.05 Hz), 6.86-6.78 (1H, m), 5.92 (1H, s); ^1^C NMR δ (CDCl₃ 75.4 MHz) 148.3, 131.7, 129.3 and 121.5.

2.7.2.4.2 Optimized procedure for decarboxylation of 3,5-dichloro-4-hydroxy benzoic acid (29a) using combination of [hmim]Br/water and NaHCO₃ (Table 6, entry 29)

A mixture of 3,5-dichloro-4-hydroxy benzoic acid (29a, 0.43 g, 2.1 mmol), [hmim]Br (1.5 ml), water (8 mmol) and 20 mol% NaHCO₃ (0.42 mmol) was irradiated under focused microwave system in parts (200W, 190°C) for 20 min. The reaction mixture was worked up and purified as mentioned in section 2.7.2.1.1 and 29b was obtained in an optimum 61% yield. The spectral data (^1^H and ^1^C NMR) of above obtained 10b matched well with that obtained in section 2.7.2.4.1.

The above procedure was also followed for decarboxylation of various other aromatic acids (Table 6, entries 30-40; Table 7, entries 41-45)

4-Nitrotoluene (30b, Table 6)

Light yellow solid, m. p. 50-52°C (lit. m. p 51–54°C) [Bull et. al. (1996)], ^1^H NMR δ (CDCl₃, 300 MHz) 8.15 (2H, d, J= 8.48 Hz), 7.35 (2H, d, J=8.48 Hz), 2.48 (3H, s); ^1^C NMR δ (CDCl₃, 75.4 MHz) 146.5, 146.3, 130.1, 123.9 and 21.9.

2-Nitrotoluene (31b, Table 6)

Yellow liquid [Bull et. al. (1996)], ^1^H NMR δ (CDCl₃, 300 MHz) 7.89 (1H, d, J= 8.23 Hz), 7.44-7.40 (1H, m), 7.27 (2H, d, J=4.94 Hz), 2.52 (3H, s); ^1^C NMR δ (CDCl₃ 75.4 MHz) 149.2, 133.5, 133.0, 132.7, 126.9, 124.6 and 20.4.
3-Chloronitrobenzene (32b, Table 6)

Viscous yellow liquid [Mendonca et al. (2005)], $^1$H NMR $\delta$ (CDCl$_3$, 300 MHz) 8.14 (1H, s), 8.07 (1H, d, $J=8.48$ Hz), 7.62 (1H, d, $J=8.48$ Hz), 7.46-7.41 (1H, m); $^{13}$C NMR $\delta$ (CDCl$_3$, 75.4 MHz) 148.8, 135.4, 134.7, 130.4, 123.8 and 121.7.

The compounds 33-36b were detected on GC-MS basis (Table 6, entries 33-36).

Diphenylmethane (37b, Table 6)

Colorless liquid [Kim and Ahn (2003)], $^1$H NMR $\delta$ (CDCl$_3$, 300 MHz) 7.27-7.25 (4H, m), 7.17-7.14 (6H, m), 3.95 (2H, s); $^{13}$C NMR $\delta$ (CDCl$_3$, 75.4 MHz) 141.1, 129.3, 128.5, 126.1 and 42.0.

The compounds 38-40b were detected on GC-MS basis (Table 6, entries 38-40).

Phenol (41b, Table 7)

Colorless liquid [Dorfner et al. (2003)], $^1$H NMR $\delta$ (CDCl$_3$, 300 MHz) 7.38-7.33 (2H, m), 7.10-7.05 (1H, m), 7.02-6.98 (2H, m), 6.80 (1H, s); $^{13}$C NMR $\delta$ (CDCl$_3$, 75.4 MHz) 156.0, 130.7, 121.9 and 116.4.

2,6-Dimethoxyphenol (42b, Table 7)

White solid, m. p 52-56°C (lit. m. p. 54-56°C) [Guillen and Ibargoitia (1998)], $^1$H NMR $\delta$ (CDCl$_3$, 300 MHz) 6.84-6.79 (1H, m), 6.61 (2H, d, $J=8.42$ Hz), 5.55 (1H, s), 3.92 (6H, s); $^{13}$C NMR $\delta$ (CDCl$_3$, 75.4 MHz) 147.6, 135.3, 119.4, 105.3 and 56.6.
2-Methoxyphenol (43b, Table 7)

\[
\text{Colorless liquid [Dorfner et al. (2003)], } \text{H} \text{NMR } \delta (\text{CDCl}_3, 300 \text{ MHz}) 7.06-7.03 (1H, m), 6.98-6.92 (3H, m), 5.98 (1H, s), 3.90 (3H, s); \text{C} \text{NMR } \delta (\text{CDCl}_3, 75.4 \text{ MHz}) 147.1, 146.1, 121.9, 120.6, 115.1, 111.3 \text{ and } 56.3.
\]

2-Hydroxyphenol (44b, Table 7)

\[
\text{White solid [Dorfner et al. (2003)], m. p. 102-103°C (lit. m. p. 105°C), } \text{H} \text{NMR } \delta (\text{CD}_3\text{COCD}_3, 300 \text{ MHz}) 7.86 (2H, s), 6.86-6.80 (2H, m), 6.71-6.65 (2H, m); \text{C} \text{NMR } \delta (\text{CD}_3\text{COCD}_3, 75.4 \text{ MHz}) 145.4, 120.6 \text{ and } 116.1.
\]

2.8 References


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$^1$H NMR (in CDCl$_3$) spectrum of 1,3-dimethyl indole (8b, Table 3)

$^{13}$C NMR (in CDCl$_3$) spectrum of 1,3-dimethyl indole (8b, Table 3)
\(^1\)H NMR (in CDCl\(_3\)) spectrum of 3,5-dimethoxy-4-hydroxy styrene (10b, Table 4)

\(^{13}\)C NMR (in CDCl\(_3\)) spectrum of 3,5-dimethoxy-4-hydroxy styrene (10b, Table 4)
$^1$H NMR (in MeOD) spectrum of 4-hydroxy stilbene (22b, Table 5)

$^{13}$C NMR (in MeOD) spectrum of 4-hydroxy stilbene (22b, Table 5)
$^1$H NMR (in CDCl$_3$) spectrum of 2,5-dichlorophenol (29b, Table 6)

$^{13}$C NMR (in CDCl$_3$) spectrum of 2,5-dichlorophenol (29b, Table 6)