Microwave promoted tandem C-C bond formation strategy in ionic liquid for synthesis of stilbenoids

4.1 Introduction:
Carbon-carbon (C-C) bond forming reactions represent one of the most vital tools for synthesis of simple as well as complex organic molecules [Heathcock et al. (1991); Meijere and Diederich (2004); Ram and Singh (2006); Goh et al. (2007); Fang et al. (2010)]. For instance, various C-C bond forming processes have been practiced on an industrial scale for the production of commercially important compounds such as naproxen [Stinson (1999)] and octyl methoxyccinnamate [Eisenstadt (1998)]. This has further been strengthened by the 2010 Nobel Prize to Richard F. Heck, Ei-ichi Negishi and Akira Suzuki for their pioneering work on Pd-catalysis leading to C-C bond formation. Consequently, realization of novel and ecofriendly strategies allowing access for construction of C-C bond is considered to be one of the grand goals of organic synthesis [Tietze (1996); Ganem (2009)].

In this context, ionic liquids (ILs), microwave (MW) and tandem/domino synthesis [Tietze (1996)] have turned out to be elegant approaches for synthetic organic chemists to accomplish formation of C-C bond. In particular, tandem synthesis improves the efficacy of the reaction by switching multiple steps into single operation and thereby avoiding isolation and purification steps for the intermediates [Sharma (2010); Prakash et al. (2011)]. Furthermore, such an approach provides an opportunity for the synthesis of bioactive molecules including stilbenes even from unfuctionalized precursors.

The stilbene moiety constitutes an important core unit of several biologically active molecules [Baur and Sinclair (2006)] besides having exciting applications in the field of optoelectronics and light harvesting energy cascade systems. For instance, various stilbenes such as resveratrol, DMU-212, pterostilbene, combretastatin etc. are widely present in nature and possess wide range of biological activities [Alonso et al. (2009)].

4.2 Importance of stilbenoids:
Stilbene and their derivatives commonly known as stilbenoids possess a vast number of bioactivities including applications in materials and medicinal chemistry domains. Some of these are briefly discussed below:
4.2 Bioactivity of stilbenoids:

4.2.1 Resveratrol and its methoxylated analogues (DMU-212 and pterostilbene):
Resveratrol \((trans-3,4',5\text{-tri}h\text{ydroxy}stilbene, \text{Figure 1})\) is a naturally occurring phytoalexin, found in more than 70 plant species including fruits like grapes, peanuts and pines. In recent years, this phenolic compound has considered worldwide attention of scientific community because of its plethora of biological activities [Aggarwall and Shishodia (2006); Kumar (2007); Rocha \textit{et al}. (2008); Alonso \textit{et al}. (2009)] such as antioxidant, radioprotective, phytoestrogen, antibacterial and antifungal activity etc. Its therapeutic potential includes the chemoprevention of cancer, inflammation, ageing, obesity, cardiovascular diseases and neurodegeneration [Kovacic and Somanathan (2010)]. The low rate of coronary heart diseases in France compared to other western countries despite the similar risk factors (i.e. high animal fat intake, low exercise level and high rate of smoking) has been called the ‘French Paradox’. Studies revealed that French have the highest consumption of wine as compared to other countries. Later on, it was found that wine contains resveratrol which inhibits the synthesis of thromboxane in platelets and modulate the synthesis and secretion of lipoproteins in animals and human cell lines.

In addition, various methoxylated analogues of resveratrol have been explored as novel chemotherapeutic agents against various cancer cell lines. In particular, DMU-212 \((\text{trans-3,4',5-tetramethoxystilbene, Figure 1})\) has recently emerged as a strong candidate exhibiting more potent anticancer activity than resveratrol [Sale \textit{et al}. (2005)]. Similarly, pterostilbene \((\text{trans-4-hydroxy-3',5'-dimethoxystilbene, Figure 1})\), is abundant in grapes and red wine, possessing antioxidant activity. The antioxidant activity of pterostilbene was demonstrated \textit{in vitro} by its inhibition of methyl linoleate oxidation [Rimando \textit{et al}. (2002)]. Besides this, pterostilbene was found to be cytotoxic against a number of cancer cell lines including human breast cancer (ED\textsubscript{50}: 13.6 \mu M) and murine lymphoid neoplasma (ED\textsubscript{50}: 10.1 \mu M) [Rimando \textit{et al}. (1994)].
4.2.1.2 Combretastatin A-4 (CA-4) and its naphthyl analogues as potential antineoplastic agents:

Combretastatin A-4 (cis-3-hydroxy-3',4,4',5'-tetramethoxystilbene) has been found to be a cytotoxic agent that strongly inhibits the tubulin polymerization by binding to the colchicine site [Tozer et al. (2002)]. This compound is capable of eliciting irreversible vascular shutdown within solid tumors, leaving normal vasculature intact [Hamel and Lin (1983)]. In addition, a number of structurally related CA-4 derivatives were also reported to possess potent bioactivities. For example, Maya et al. studied the cytotoxic structure activity relationship of naphthalene analogues of CA-4 [Maya et al. (2005)]. It was found that replacement of 3-hydroxy-4-methoxyphenyl ring of CA-4 with 2-naphthalene ring results in compounds with potency comparable to that of the parent compound i.e CA-4. On the other hand, when naphthalene ring replaces the 3,4,5-trimethoxyphenyl moiety of CA-4, the cytotoxic activity is largely decreased. These results show that the naphthalene ring is a good surrogate for the 3-hydroxy-4-methoxyphenyl ring of CA-4 (Figure 2).

Similarly, 5-membered heterocyclic analogues of CA-4 were also reported to possess antineoplastic activities [Ohsumi et al. (1998)]. Likewise, quinoline and quinoxaline analogous of combretastatin are reported as potent cytotoxic agents and inhibitors of tubulin polymerization [Perez-Melero et al. (2004)].

4.2.1.3 Conjugated stilbenoids for Alzheimer’s detection:

Various conjugated stilbenoids such as distyrilbenzenes have been used as non invasive probes for the detection of Alzheimer’s disease [Lee et al. (2001); Flaherty et al. (2007)]. Some of the stilbenoids showing strong binding and excellent staining properties for infected brain sections are given in Figure 3.
In addition to various biological activities of stilbenoids, these compounds also find applications in material science as well.

4.2.2 Applications of stilbenoids in material science:
The conjugated stilbenes [Kalanoor et al. (2009); Sharma et al. (2010)] are unique scaffolds as these combine the properties of both conventional polymers as well as inorganic semiconductors. Moreover, the good emission properties, greater ease of purification, crystalline structures of stilbenoids have made them an attractive component of machines which convert information from light to electrical energy and vice-versa [Hulvat et al. (2005)]. For instance, a stilbene based framework (cis-4,4'-bis(diarylarnino)stibene-fluorene hybrid) has been reported to exhibit a sharp blue fluorescence at 464 nm (Scheme 1) [Wei and Chen (2007)].

Thus, use of stilbenes is being increasingly explored in organic light emitting diodes (OLED’s), solar cells [Goodson et al. (1997); Wei and Chen (2007)] and a host of other optoelectronic devices.

4.3 Reported methods for C-C bond formation: Synthesis of stilbenoids
The remarkable biological and industrial importance of substituted stilbenes has prompted intensive efforts towards development of their synthetic methodologies [Filmon et al. (2004); Kumar (2007); Sinha et al. (2007, 2010); Shirakawa et al. (2011)]. Some of strategies for the synthesis of stilbenoids via C-C bond formation are:
Microwave promoted tandem…..

- Wittig reaction
- Modified Perkin reaction
- Suzuki coupling
- Negishi coupling
- Heck coupling

A brief description of above approaches is given below.

4.3.1 Wittig reaction:

The Wittig reaction [Wittig and Schollkopf (1954)] is the reaction of an aldehyde or ketone with a triphenyl phosphonium ylide (often called a Wittig reagent) to give the substituted alkene along with triphenylphosphine oxide as a by product. The reaction usually furnishes the mixture of both Z and E isomers which requires various techniques including crystallization for their separation. For instance, Roberti et al. prepared a number of stilbene derivatives through Wittig approach which were tested in vitro for cell growth inhibition as well as for the ability to induce apoptosis in HL60 promyelocytic leukemia cells (Scheme 2) [Roberti et al. (2003)].

![Scheme 2](image)

Recently, a one pot Wittig approach promoted by nickel nanoparticles (NiNPs) for the synthesis of biologically active stilbenes such as resveratrol, DMU-212 etc. using inexpensive benzyl alcohols as phosphorus ylide partners have been disclosed (Scheme 3) [Alonso et al. (2009)].

![Scheme 3](image)

**Scheme 3:** Reagents and conditions: (a) PBr₃, CH₂Cl₂, 0°C to r.t., overnight; (b) PPh₃, toluene, reflux, 6 h; (c) n-BuLi, THF, 0 °C, 20 min; (d) NiNPs, THF, reflux, 12 h.
4.3.2 Modified Perkin reaction:
Sinha et al. reinvestigated the classical Perkin reaction whereby simultaneous condensation-decarboxylation provides a convenient one pot access to various bioactive stilbenes from hydroxy substituted benzaldehydes and phenylacetic acids under MW irradiation (Scheme 4) [Sinha et al. (2007)].

\[
\text{R}^1\text{CHO} + \text{R}^7\text{COOH} \overset{\text{Piperidine-1-methylimidazole, PEG-200, MW}}{\longrightarrow} \text{R}^1\text{R}^6\text{R}^9\text{R}^3\text{R}^4\text{R}^6\text{R}^8
\]

where at least one of \( R^1 \) or \( R^2 \) or \( R^5 \) or \( R^6 \) or \( R^8 \) or \( R^{10} = \text{OH} \)
and \( R^1, R^{10} = \text{H, OMe, -OCH}_2\text{O-, OH, Cl, NO}_2 \) etc.

Scheme 4

4.3.3 Suzuki coupling:
The Suzuki cross-coupling of an aryl boronic acid and vinyl bromide has been employed for the stereo-selective synthesis of \( Z \) and \( E \) isomers of CA-4 [Gaukroger et al. (2001)]. \( Z \)-vinyl bromide was used for the synthesis of corresponding \( Z \)-stilbene while \( E \)-vinyl bromide was used for the synthesis of \( E \)-stilbene (Scheme 5).

\[
\text{ArBr} + \text{ArB(OH)}_2 \overset{\text{Pd(PPh}_3)_4, \text{Na}_2\text{CO}_3, \text{DME}}{\longrightarrow} \text{Ar}-\text{OCH}_3
\]

Scheme 5

4.3.4 Negishi coupling:
Kabir et al. reported a synthetic route for the Pd-catalyzed cross-coupling of an arylzinc reagent with arylvinyl iodides (Negishi coupling) for the efficient and selective preparation of \( E \)-stilbenes and their analogues (Scheme 6) [Kabir et al. (2007)].

\[
\text{ArBr} \overset{n\text{-BuLi, i, ZnCl}_2, \text{THF}}{\longrightarrow} [\text{ArZnBr}] \overset{\text{Pd}_2(\text{dba})_3, 2 \text{ mol%}}{\longrightarrow} \text{Ar-} \text{OCH}_3
\]

Scheme 6
4.3.5 Heck coupling:
Heck reaction (Mizoroki–Heck reaction) is a Pd-catalysed arylation of olefins and is one of the most important processes in synthetic organic chemistry for the construction of C-C bond. In this reaction, organic halides (aryl or vinyl) react with olefins (styrenes, acrylic acids etc.) in the presence of catalytic amounts of palladium and a base to form the substituted olefins including stilbenoids (Scheme 7). Generally, this reaction occurs efficiently mainly in polar solvents (such as DMF, NMP, DMSO etc.) and requires long reaction time (8–72 h) at temperature ranging from 80-140°C [Deshmukh et al. (2001)].

\[
\begin{array}{c}
\text{R}_1X + \text{R}_2 \xrightarrow{\text{Pd-catalyst}} \text{R}_1\text{R}_2 \\
\text{X} = \text{Br, I, Cl, OTf etc.} \\
\text{R}_1 = \text{Aryl, vinyl etc.} \\
\text{R}_2 = \text{Aryl, COOEt, COOH etc.}
\end{array}
\]

Scheme 7

4.4 Non-conventional methodologies for C-C bond formations: Green context of Heck reaction
With the increasing environmental awareness, considerable efforts have been directed to search environment friendly coupling processes. Consequently, designing of new methodologies which make the already known chemical transformations simpler, faster, cheaper, greener and in general, more efficient are on rise [Alonso et al. (2005)]. In particular, use of non-classical solvents (such as ILs, water and supercritical CO\textsubscript{2} etc.), energy efficient MW, idea of atom-economic reactions, replacement of expensive and unstable coupling partner with stable and inexpensive precursors may also be a useful concept in helping to promote thinking in the direction of sustainable chemistry. A review by Alonso et al. demonstrates the possibilities of development of various non-conventional conditions [Alonso et al. (2005)] for Heck reaction by working at different levels as mentioned below in Scheme 8.

\[
\begin{array}{c}
\text{ArX} + \text{R} \xrightarrow{\text{Transition-metal catalyst}} \text{ArR} \\
\text{Non-conventional conditions:} \text{Ligandless, solid support, supercritical fluids, ionic liquids, aqueous solvents, microwave, ultrasound, high pressure, micelles, electrochemical activation, nanofiltration, microreactors, etc.}
\end{array}
\]

Scheme 8
A brief remark to some of the green techniques (such as MW, ILs etc.) employed in the Heck reaction is given below.

4.4.1 Microwave as an efficient source of energy for Heck reaction:

Microwave-promoted synthesis is an area of increasing research interest as evidenced by the number of papers and recent reviews appearing in the literature [Kappe (2008); Polshettiwar and Varma (2008)]. MW heating in the Heck reaction has been found to enhance the rate of reaction significantly.

For instance, Heck coupling reaction was performed under MW heating in water using tetrabutylammonium bromide (TBAB), Na$_2$CO$_3$ as a base and low concentration of Pd catalyst (upto 500 ppb) (Scheme 9). The reaction took 5 to 10 min besides providing the products in good yields [Arvela and Ledbeater (2005)].

\[
\begin{align*}
\text{Br} & \quad \text{MW} \\
\text{Pd, H$_2$O, TBAB, Na$_2$CO$_3$} & \\
\rightarrow & \\
\text{R} & \quad \text{R}'
\end{align*}
\]

Scheme 9

The above developed methodology has further been scaled-up by the same group using an automated batch stop-flow microwave apparatus [Arvela et al. (2005)]. Similarly, Leadbeater et al. reported the scale-up of Heck reaction in open reaction vessels under MW irradiation. The reaction took place smoothly using Pd(OAc)$_2$ as a catalyst, Na$_2$CO$_3$/Bu$_3$N as bases and TBAB as an additive [Leadbeater et al. (2006)].

In another report, a rapid microwave-promoted Heck reaction of aryl halides with olefins using Pd(OAc)$_2$/K$_3$PO$_4$ catalytic system under ligand-free and solvent-free conditions is described (Scheme 10) [Du and Wang (2007)].

\[
\begin{align*}
\text{R} & \quad \text{X} \\
\text{Pd(OAc)$_2$, K$_3$PO$_4$ (1.4 eq) } \\
\text{Al$_2$O$_3$, M.W. 300 W} & \\
\rightarrow & \\
\text{R} & \quad \text{R$_1$}
\end{align*}
\]

Scheme 10
Heck coupling was also carried out in the absence of any ligand with very low catalyst loads under MW or simultaneous microwave/ultrasound irradiation [Palmisano et al. (2007)]. Recently, a novel one-pot preparation of nonsymmetrical substituted stilbenes using a two-step double Heck strategy under MW irradiation has been disclosed (Scheme 11) [Kormos and Leadbeater (2008)]. The use of MW apparatus offers ease of handling the gaseous reagents.

\[
\begin{align*}
R & = R' = \text{OCH}_3, \text{CH}_3, \text{COCH}_3 \\
X & = \text{I, Br}
\end{align*}
\]

Scheme 11

4.4.2 Heck reaction in ionic liquids:

The use of ILs in Heck reaction has received considerable attention [Bellina and Chiappe (2010)] because of high solubility as well as stability of Pd catalyst which is oftenly lost at the end of the reaction. Kaufmann and co-workers for the first time reported the application of ionic liquid [C_{16}PBu_3]Br in the Heck reaction [Kaufmann et al. (1996)]. The authors explained that IL efficiently stabilizes the Pd(0) species obtained \textit{in situ} by the reduction of Pd(II) catalyst. Thereafter, Carmichael et al. reported the use of ionic liquid [C_6Py]Cl as solvent in the Heck reaction without using any ligand [Carmichael et al. (1999)].

In the year 2000, Xiao and co-workers carried out a detail study on the imidazolium based ILs and showed that Pd(OAc)_2 reacts with imidazolium cation of [bmim]Br ionic liquid resulting in the formation of 1-butyl-3-methylimidazol-2-ylidine (bmiy) complexes of palladium (such as [PdBr(μ-Br)(bmiy)]_2 and [PdBr_2(bmiy)_2]) (Scheme 12) which were found responsible for C-C coupling [Xu et al. (2000)]. Also it was observed that Heck reaction proceeds more efficiently in [bmim]Br than in the analogous tetrafluoroborate ionic liquid i.e. [bmim]BF_4.
Microwave promoted tandem….

Many of the work on Heck reaction is related to imidazolium based ILs. In the year 2006, an interesting paper highlighting the possibility to use a Bronsted guanidine acid-base IL for Heck coupling was published (Scheme 13) [Li et al. (2006)]. The IL butyltetramethylguanidinium acetate was prepared by the neutralization of corresponding guanidine with acetic acid and used as a solvent, ligand and base in the reactions of aryl halides with styrene at 140°C.

In another report, Iranpoor et al. disclosed the use of an imidazolium based phosphinite ionic liquid (IL-OPPh2) as solvent as well as ligand in the Heck coupling reaction of aryl halides (including chlorobenzene) with styrene or butyl acrylate providing the products in high yields (Scheme 14) [Iranpoor et al. (2007)].
Recently, a task-specific ionic liquid (TSIL) based on ethanolamine-functionalized quaternary ammonium salt was designed and synthesized by Wang et al. for Heck coupling reaction [Wang et al. (2009)]. The synthesized IL acts as a base, ligand and reaction medium besides exhibiting a very high activity and recyclability (Scheme 15).

![Scheme 15](image)

Cal et al. reported the use of tetraalkylammonium ILs along with palladium nanoparticles for the coupling of deactivated and electron-rich aryl chlorides in Heck reaction [Cal et al. (2009)]. Furthermore, to avoid the catalysts leaching out of the IL system, significant efforts have been made to enhance the solubility of the catalysts using supported ILs, ionic polymers etc. [Ma et al. (2008); Bellina and Chiappe (2010)].

4.4.3 Combination of ionic liquids and microwave in Heck reaction:

The conjunction of ILs and MW irradiation as a non-conventional heating source has shown advantages in the Heck reaction when compared to conventional synthetic procedures for the generation of fast, efficient and environment friendly synthetic methodologies [Palou (2010)]. For example, Xie et al. disclosed the Pd/C-catalyzed Heck coupling of aryl halides with styrenes in 1-octanoyl-3-methylimidazolium tetrafluoroborate ([omim]BF₄) under MW irradiation in very short reaction time (1.5-2.0 min) (Scheme 16) [Xie et al. (2004)]. The IL containing catalytic system was used five times with a little loss in activity.

![Scheme 16](image)

Similarly, MW heating in sealed tube was found to accelerate the Heck reaction of aryl halides with n-butyl acrylate in [bmim]PF₆ [Vallin et al. (2002)]. In addition to MW,
combination of ultrasonic irradiation with IL has also been used in the Heck reaction [Deshmukh et al. (2001)].

4.4.4 Alternative stable coupling partners for styrenes:

As mentioned earlier, Heck reaction is usually carried out by reacting organic halides with olefinic compounds in the presence of palladium catalyst and a suitable base. Usually, organic halides are commercially available or can be synthesized easily. In addition, various arylating agents such as aromatic carboxylic acids, anhydrides and esters [Stephan et al. (1998), Myers et al. (2002), Alonso et al. (2005)] etc. have been introduced in place of aryl halides for the Heck coupling with styrenes.

On the other side, substituted styrenes (other coupling partner in the Heck reaction) are not readily available and require special attentions for their storage due to their propensity towards polymerization. Additionally, their synthesis and isolation are also quite tedious. Therefore, realization of a tandem Heck reaction from inexpensive and stable starting material via *in situ* formation of styrenes followed by coupling with aryl halides would be practically useful as such a strategy would eliminate the additional isolation and purification steps for the intermediate styrenes which are otherwise very much prone to polymerization. Recently, a tandem synthesis of stilbenoids *via* dehydrohalogenation-Heck coupling strategy using aryl-substituted alkyl bromides (Scheme 17) as *in situ* source of styrenes has been furnished in literature [Saiyed and Bedekar (2010)].

\[
\begin{align*}
\text{Dehydrohalogenation} & \quad \text{Wittig} \\
\begin{array}{c}
\begin{array}{c}
\text{Ar} \\
\text{Ar}
\end{array}
\end{array} & \quad \begin{array}{c}
\begin{array}{c}
\text{Ar}\text{CHO} \\
\text{Ph}_3\text{PCH}_3\text{Br}
\end{array}
\end{array} \\
\begin{array}{c}
\begin{array}{c}
\text{K}_2\text{CO}_3 \\
\text{DMA, 140°C}
\end{array}
\end{array} & \quad \begin{array}{c}
\begin{array}{c}
\text{Ph}_3\text{PCH}_3\text{Br}
\end{array}
\end{array} \\
\begin{array}{c}
\begin{array}{c}
\text{Ar} \\
\text{Ar}\text{CHO}
\end{array}
\end{array} & \quad \begin{array}{c}
\begin{array}{c}
\text{HCHO}
\end{array}
\end{array} \\
\begin{array}{c}
\begin{array}{c}
\text{K}_2\text{CO}_3 \\
\text{DMA, 140°C}
\end{array}
\end{array} & \quad \begin{array}{c}
\begin{array}{c}
\text{ArCH}_3\text{P}(\text{OPh})_3\text{Br}
\end{array}
\end{array}
\end{align*}
\]

\[
\text{Heck} \\
\begin{array}{c}
\begin{array}{c}
\text{Ar}
\end{array}
\end{array} & \quad \text{Ligand} \\
\begin{array}{c}
\begin{array}{c}
\text{K}_2\text{CO}_3 \\
\text{Ligand}
\end{array}
\end{array} & \quad \begin{array}{c}
\begin{array}{c}
\text{DMA, 140°C}
\end{array}
\end{array} \\
\begin{array}{c}
\begin{array}{c}
\text{X-Ar'}
\end{array}
\end{array} & \quad \text{Ligand}
\]

\[
\begin{array}{c}
\begin{array}{c}
\text{Ar}
\end{array}
\end{array} & \quad \text{NH}_2
\]

\text{Scheme 17}
However, such substituted bromides itself are sometimes not commercially available or synthesized by the bromination of corresponding arylalcohols using PBr$_3$ etc. [Alonso et al. (2009)].

On the other side, arylalcohols (including 2° benzylic alcohols) have not received any attention as an in situ source of styrenes (via dehyration instead of known dehydrobromination route) in tandem Heck strategy for the synthesis of stilbenoids. The main reason is that dehydration of arylalcohols is generally carried out in the presence of acid catalysts whereas Heck coupling step requires basic conditions and therefore cross contamination of the reagents/catalysts of the two steps is a major problem while designing the above tandem process for stilbenoids starting from arylalcohols. Moreover, literature survey also revealed that arylalcohols under Heck like conditions preferred oxidation under palladium catalysis [Crawley et al. (2009)].

Thus, it is evident from above discussion that there is not any tactic accessible for one pot/tandem synthesis of stilbenoids from arylalcohols acting as budding and inexpensive source of styrenes. For instance, Heck reaction for the synthesis of stilbenoids from arylalcohols involves dehydrohalogenation route [Saiyed and Bedekar (2010)], for which initial bromination of arylalcohols followed by column purification is required. Similarly, Wittig approach for stilbenoids (from arylalcohols) requires a multistep protocol [Alonso et al. (2009)] besides need of protection–deprotection manipulation in case of hydroxyl substituents.

In this context, it was envisaged to develop a tandem dehydrative-Heck approach that not only utilizes environmental friendly ILs and inexpensive precursors like arylalcohols (as a source of styrenes) but also simultaneously dispenses with the requirement of multiple steps and protection-deprotection manipulations.

4.5 Results and Discussion:

In order to develop a C-C bond formation strategy for the synthesis of stilbenoids possessing biologically active naphthyl scaffolds [Maya et al. (2005)], a tandem route involving dehydration of arylalcohols to generate the styrenes in situ followed by a Pd catalyzed Heck coupling with aryl halides appeared attractive. Amongst the several available approaches for dehydration of arylalcohols, it was planned to use neutral ionic liquid [hmim]Br as it has been found to be an efficient dehydrating agent [Kumar et al. (2008)] as mentioned earlier in the first objective of this thesis work. In this context, it was
imperative to find out the suitable conditions for Heck coupling reaction which could simultaneously be compatible with the IL used to generate styrenes besides its role as a solvent.

Initially, 4-iodoanisole (0.2 g, 0.85 mmol, 1 equiv.) was allowed to react with 1-(naphthalen-2-yl)ethanol (1a, 1.28 mmol, 1.5 equiv.) in [hmim]Br (dehydrating agent as well as solvent) using Pd(OAc)$_2$ (4 mol%) as a catalyst, PPh$_3$ (5 mol%) as a ligand and Et$_3$N (1.28 mmol, 1.5 equiv.) as a base (Table 1, entry 1) under MW irradiation (120W, 150°C).

After completion of reaction, the crude product was analyzed through HPTLC method and the expected stilbene i.e. 2-[(E)-2-(4-methoxyphenyl)ethenyl]naphthalene (1b; confirmed with reference standard [Saiedy and Bedekar (2010)]) was obtained in only 8% yield (Figure 4 and Table 1, entry 1) along with intermediate napthyl styrene (dehydrated product of 1a). To further increase the yield of 1b, various other organic bases (such as Bu$_3$N, piperidine & DBU) and inorganic bases (such as Cs$_2$CO$_3$, K$_2$CO$_3$, NaOAc, NH$_4$OAc

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Eq.</th>
<th>Time (min)</th>
<th>Yield $^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Et$_3$N</td>
<td>1.5</td>
<td>40</td>
<td>8</td>
</tr>
<tr>
<td>2</td>
<td>Br$_3$N</td>
<td>1.5</td>
<td>40</td>
<td>30</td>
</tr>
<tr>
<td>3</td>
<td>Piperidine</td>
<td>1.5</td>
<td>40</td>
<td>32</td>
</tr>
<tr>
<td>4</td>
<td>DBU</td>
<td>1.5</td>
<td>40</td>
<td>5</td>
</tr>
<tr>
<td>5</td>
<td>Cs$_2$CO$_3$</td>
<td>1.5</td>
<td>40</td>
<td>6</td>
</tr>
<tr>
<td>6</td>
<td>K$_2$CO$_3$</td>
<td>1.5</td>
<td>40</td>
<td>7</td>
</tr>
<tr>
<td>7</td>
<td>NaOAc</td>
<td>1.5</td>
<td>40</td>
<td>nd</td>
</tr>
<tr>
<td>8</td>
<td>NH$_4$OAc</td>
<td>1.5</td>
<td>40</td>
<td>13</td>
</tr>
<tr>
<td>9</td>
<td>HCOO$^-$Na</td>
<td>1.5</td>
<td>40</td>
<td>69 (56)$^c$</td>
</tr>
<tr>
<td>10</td>
<td>HCOO$^-$NH$_4$</td>
<td>1.5</td>
<td>40</td>
<td>(41)$^c$</td>
</tr>
<tr>
<td>11</td>
<td>HCOO$^-$K</td>
<td>1.5</td>
<td>40</td>
<td>(52)$^c$</td>
</tr>
<tr>
<td>12</td>
<td>HCOO$^-$Na</td>
<td>1</td>
<td>40</td>
<td>(50)$^c$</td>
</tr>
<tr>
<td>13</td>
<td>HCOO$^-$Na</td>
<td>2.5</td>
<td>40</td>
<td>(52)$^c$</td>
</tr>
<tr>
<td>14</td>
<td>HCOO$^-$Na$^+$ K$_2$CO$_3$</td>
<td>1.5+1.5</td>
<td>15</td>
<td>(59)$^c$</td>
</tr>
<tr>
<td>15</td>
<td>HCOO$^-$Na$^+$ Piperidine</td>
<td>1.5+1.5</td>
<td>15</td>
<td>(64)$^c$</td>
</tr>
<tr>
<td>16</td>
<td>HCOO$^-$Na$^+$ Piperidine</td>
<td>1.5+1.0</td>
<td>15</td>
<td>(69)$^c$</td>
</tr>
<tr>
<td>17</td>
<td>HCOO$^-$Na$^+$ Piperidine</td>
<td>1.5+0.5</td>
<td>15</td>
<td>(65)$^c$</td>
</tr>
</tbody>
</table>

$^a$CEM monomode microwave; General conditions: 4-iodoanisole (0.85 mmol), 1a (1.28 mmol), Pd(OAc)$_2$ (4 mol%), PPh$_3$ (5 mol%), base, [hmim]Br (1.5 g), 120W, 150°C; $^b$Yields determined by HPTLC with reference standard; $^c$Yield of isolated product 1b.
Microwave promoted tandem...... Chapter 4

& HCOONa) in place of Et$_3$N were rapidly screened with the help of developed HPTLC method (Figure 4 and Table 1, entries 2-9). Out of these, HCOONa was surprisingly found to increase the yield of 1b up to 69% (56% isolated yield after column purification, Table 1, entry 9).

![HPTLC image](image)

(i)

Figure 4: (i) HPTLC CCD image at 254 nm: standard tracks (A-E) of 1b at different concentrations, samples tracks 1-9 indicating formation of 1b (Table 1); (ii) 3D HPTLC densitogram of samples 1-9 (yields were expressed in terms of % peak area, wherein yield varies from 0 to 69%) (Table 1, entries 1-9)

Note: [It is pertinent to mention that the above crude product (Table 1, entry 1) could not be analyzed through commonly used C18 reverse phase HPLC analysis due to its precipitation in the mobile phase (such as ACN, MeOH, H$_2$O etc). Similarly, GC-MS analysis of the same was also unsuccessful probably due to low volatility; hence HPTLC analysis was preferred over HPLC or GC-MS.]
Replacement of HCOONa with other formate salts such as HCOONH₄ (Table 1, entry 10) and HCOOK (Table 1, entry 11) provided the corresponding product in comparatively lower yields i.e. 41% and 52% (isolated) respectively. On the other side, use of 1 equiv. or 2.5 equiv. of HCOONa in place of 1.5 equiv. was not found to be suitable for further enhancement in the yield of 1b (Table 1, entries 12-13). Later on, it was thought to explore the synergistic combination of two bases, since a number of earlier reports have demonstrated the efficacy of such a combination [Peng and Song (2003); Sinha et al. (2007)]. Consequently, combinations of HCOONa (1.5 equiv.) with other bases like, K₂CO₃ and piperidine were screened (Table 1, entries 14-17).

Thus, a base combination of HCOONa (1.5 equiv.)-piperidine (1.5 equiv.) not only increased the reaction performance as 1b was isolated in 64% yield (Table 1, entry 15), but also reduced the reaction time to 15 min from 40 min (Table 1, entry 9). In addition, use of
1 equiv. of piperidine in place of 1.5 equiv. in above combination further improved the yield as 1b was obtained in 69% yield (Table 1, entry 16).

Subsequently, a detailed optimization study was conducted to evaluate the effect of other ILs, Pd catalysts and additives (Table 2). However, use of ILs such as [bmim]BF₄ and [bmim]PF₆ (commonly used in the Heck reaction) in place of [hmim]Br provided 1b in very low yield (Table 2, entries 2-3) due to their inefficiency for the dehydration of 1a. Also, it was interesting to note that replacement of IL with molecular solvent such as DMF (Table 2, entry 5) did not lead to the formation of corresponding 1b thus emphasizing the crucial role of IL in the above tandem process. In order to further increase the yield of 1b, the above reaction was performed with various other Pd catalysts like PdCl₂, Pd(PPh₃)₄, Pd(CF₃COO)₂ and PdCl₂(PPh₃)₂, wherein, PdCl₂(PPh₃)₂ was found to increase the yield of the reaction upto 74% (Table 2, entry 9).

Here it is pertinent to mention that along with formation of expected stilbene 1b, α-arylated was observed as side product. In order to suppress the formation of α-arylated side product, additives such as LiCl, Ag₂O, Ag₂CO₃ were tried [Sharma et al. (2010)], wherein use of LiCl (8 mol%) was found to enhance the yield of 1b upto 78% (Table 2, entry 10).

To ascertain the specific role of MW, reaction of 1a was also performed under conventional heating (oil bath, 150°C), however, the corresponding 1b was obtained only in 20% yield even after 14 h (Table 2, entry 13), thus unequivocally demonstrating the role of MW in effectively bringing out the tandem dehydrative-Heck coupling of 1a in short reaction time (15 min v/s 14 h).

Mechanistically, it is presumed that, an incipient styrene (formed in situ via IL assisted dehydration) [Kumar et al. (2008)] simultaneously undergoes Pd catalyzed cross coupling with aryl halide leading to formation of stilbenes in one-pot (Figure 5) [Sharma et al. (2010)].
To further elaborate the scope of this approach, a wide range of substituted arylalkanols were subjected to the above optimized condition using arylhalide as coupling partners and the corresponding stilbenes were obtained in good yields (Table 3).

![Table 3. Ionic liquid assisted tandem synthesis of stilbenes from arylalcohols][1]

As would be evident from Table 3, the methodology was found effective for the synthesis of diverse array of stilbenes possessing electron donating as well as electron withdrawing groups either on the arylalcohol or on the aryl halide. Consequently, various polyaromatic

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[1]: https://example.com/table3.png
stilbenoids possessing biologically important 2-naphthyl moiety were easily accessed in good yields (Table 3, entries 1-5) from corresponding arylalcohols. Under similar conditions, acetylated derivative of alcohols underwent novel one pot tandem hydrolysis-dehydration-Heck coupling reaction and the corresponding stilbenes were obtained in good yields (Table 3, entries 6-7).

In addition, the developed methodology was also found applicable to provide the hydroxyl substituted stilbenes (Table 3, entries 2, 8 and 10) in very good yields without any protection-deprotection manipulations.

4.6 Conclusion:

In summary, a new one pot strategy for the preparation of stilbenoids involving a tandem dehydrative-Heck coupling assisted by neutral ionic liquid is developed. The method utilizes readily available, stable and inexpensive arylalcohols as in situ source of styrenes and do not require any inert atmosphere. The developed method is an efficient, atom economic and ecofriendly alternative to the prevalent multi-step approaches as it eliminates the need for the isolation of polymerization prone styrenes as well as protection-deprotection manipulations in case of hydroxyl substituents.

4.7 Experimental Section:

4.7.1 General Procedure:

The palladium catalysts and other reagents were purchased from Acros, Aldrich and Merck and used as such. Aryl alcohols were either obtained commercially or synthesized by the reduction of corresponding acetophenones [Botteghi et al. (2003)]. The ILs were purchased (Merck & Alfa Aesar) or synthesized ([hmim]Br, [bmim]OH) using earlier reported methods [Nockemann et al. (2005); Ranu and Banerjee (2005)]. The purity of ILs was checked by NMR before use. All reactions were carried out in the absence of inert atmosphere. The solvents used for isolation/purification of compounds were obtained from commercial sources (Merck) and used without further purification. Column chromatography was performed using silica gel (Merck, 60-120 mesh size). 1H (300 MHz) and 13C (75.4 MHz) NMR spectra were recorded on a Bruker Avance-300 spectrometer. The following abbreviations were used to designate chemical shift multiplicities: s = singlet, br = broad, d = doublet, t = triplet, m = multiplet. The 13C NMR spectra are proton decoupled. CEM Discover® focused microwave (2450 MHz, 300W) was used wherever mentioned. The temperature of reactions in MW 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 an oil bath, the temperature of reaction mixture was monitored by an inner thermometer. HRMS-ESI spectra were determined using micromass Q-TOF ultima spectrometer. The melting points were determined on a digital Barnsted Electrothermal 9100 apparatus. The visualization of TLC plates particularly in case of polyaromatic stilbenes was best monitored in UV chamber.

4.7.2 HPTLC analysis:
HPTLC analysis was performed on a Camag HPTLC system equipped with an automatic TLC sampler (ATS 4), TLC scanner 3 (winCATS version 1.2.3) with UV cabinet and twin trough glass tank (20×20 cm). Normal phase TLC plate (Si 60F254) from Merck was used. The samples were applied using automated TLC sampler in 6 mm bands at 15 mm from the bottom and 13 mm space between the two bands. The chamber used for developing the plate was pre-saturated with mobile phase, hexane: EtOAc: AcOH (38.9:1:0.1, v/v/v) for 30 min. The analysis was done at room temperature (25°C ± 2°C). Scanning of the plate was done in reflectance/absorbance mode at 254 nm.

4.7.3 Optimization of reaction conditions:
4.7.3.1 Tandem synthesis of 2-[(E)-2-(4-methoxyphenyl)ethenyl]naphthalene (1b) from 1-(naphthalen-2-yl)ethanol (1a) and 4-iodoanisole using Pd(OAc)$_2$, PPh$_3$ and Et$_3$N as a base in [hmim]Br under microwave irradiation (Table 1, entry 1)
A mixture of 4-iodoanisole (0.2 g, 0.85 mmol), 1-(naphthalen-2-yl)ethanol (0.22 g, 1.28 mmol), Pd(OAc)$_2$ (4 mol%), PPh$_3$ (5 mol%) and Et$_3$N (1.28 mmol) in [hmim]Br (1.5 g) was irradiated under focused MW (120W, 150°C) for 40 min. After completion, water (20 ml) was added to the reaction mixture and extracted with ethyl acetate (2×25 ml). The combined organic layer was washed with water (2×10 ml), brine (1×10 ml), dried over anhydrous Na$_2$SO$_4$ and vacuum evaporated to obtain a crude product which was analyzed by HPTLC (as given in section 4.7.2) in comparison to a reference standard providing a conversion yield of 8%.

4.7.3.2 Tandem synthesis of 1b from 1a with Pd(OAc)$_2$, PPh$_3$ in [hmim]Br using different bases such as Bu$_3$N, piperidine, DBU, Cs$_2$CO$_3$, K$_2$CO$_3$, NaOAc, NH$_4$OAc & HCOONa in place of Et$_3$N (Table 1, entries 2-9):
The reactions were performed in the same manner as given above in section 4.7.3.1 using [hmim]Br with Bu$_3$N, piperidine, DBU, Cs$_2$CO$_3$, K$_2$CO$_3$, NaOAc, NH$_4$OAc and HCOONa
replacing Et\textsubscript{3}N in equal molar amounts in each case. The reactions upon completion followed by work up (same as in section 4.7.3.1) and upon HPTLC analysis as given in section 4.7.2 provided 1b with conversion yields of 30, 32, 5, 6, 7, 0, 13 and 69% in the case of Bu\textsubscript{3}N, piperidine, DBU, Cs\textsubscript{2}CO\textsubscript{3}, K\textsubscript{2}CO\textsubscript{3}, NaOAc, NH\textsubscript{4}OAc and HCOONa respectively.

**4.7.3.3 Tandem synthesis of 1b from 1a with Pd(OAc)\textsubscript{2}, PPh\textsubscript{3} in [hmim]Br using different bases such as HCOONa, HCOONH\textsubscript{4} and HCOOK in place of Et\textsubscript{3}N (Table 1, entries 9-13) (with column purification)**

In case of entries 9-11 (Table 1), the reactions were performed in the same manner as given in section 4.7.3.1 using HCOONa, HCOONH\textsubscript{4} and HCOOK replacing Et\textsubscript{3}N in equal molar amounts i.e. 1.28 mmol in each case. After the completion of reaction, each of the reaction mixture was worked up as in section 4.7.3.1. The obtained crude mixture of each reaction was subsequently purified by column chromatography on silica gel (60-120 mesh size) using 2% ethylacetate in hexane. The above experiments provided 1b in 56, 41 and 52% yields in the case of HCOONa, HCOONH\textsubscript{4} and HCOOK respectively (Table 1, entries 9-11).

In the above procedure, use of 0.85 mmol of HCOONa (Table 1, entry 12) or 1.71 mmol of HCOONa (Table 1, entry 13) provided 1b in inferior yields. Thus, 1.28 mmol of HCOONa was found to be the optimum base and used in all the subsequent experiments. The product 1b was confirmed by NMR spectroscopy as given below.

**2-[(E)-2-(4-Methoxyphenyl)ethenyl]naphthalene (1b) [Saiyed and Bedekar (2010)]**

\[
\text{White solid, m.p. 173-175°C, } ^1\text{H NMR (300 MHz, CDCl}_3\); } \delta \text{ (ppm) 7.85-7.74 (5H, m), 7.54-7.48 (4H, m), 7.26-7.14 (2H, m), 6.97-6.94 (2H, m), 3.87 (3H, s); } ^{13}\text{C NMR (75.4 MHz, CDCl}_3\); } \delta \text{ (ppm) 159.8, 135.6, 134.2, 133.3, 130.6, 129.0, 128.6, 128.3, 128.2, 128.1, 127.1, 126.6, 126.5, 126.0, 123.9, 114.6 and 55.7.}

**4.7.3.4 Effect of K\textsubscript{2}CO\textsubscript{3} in combination with HCOONa in place of HCOONa alone on the tandem synthesis of 1b from 1a with Pd(OAc)\textsubscript{2}, PPh\textsubscript{3} in [hmim]Br (Table 1, entry 14):**

A mixture of 4-iodoanisole (0.2 g, 0.85 mmol), 1-(naphthalen-2-yl)ethanol (0.22 g, 1.28 mmol), Pd(OAc)\textsubscript{2} (4 mol%), PPh\textsubscript{3} (5 mol%), HCOONa (0.87 g, 1.28 mmol) and K\textsubscript{2}CO\textsubscript{3} (1.28 mmol) in [hmim]Br (1.5 g) was irradiated under focused MW (120W, 150°C) for 15
min. The reactions upon completion followed by work up and purification as given in section 4.7.3.3 provided 1b in 59% yield.

4.7.3.5 Effect of piperidine in combination with HCOONa in place of HCOONa alone on the tandem synthesis of 1b from 1a with Pd(OAc)$_2$, PPh$_3$ in [hmim]Br (Table 1, entries 15-17):

A mixture of 4-iodoanisole (0.2 g, 0.85 mmol), 1-(napthalen-2-yl)ethanol (0.22 g, 1.28 mmol), Pd(OAc)$_2$ (4 mol%), PPh$_3$ (5 mol%), HCOONa (0.87 g, 1.28 mmol) and piperidine (1.28 mmol) in [hmim]Br (1.5 g) was irradiated under focused MW (120W, 150°C) for 15 min. The reactions upon completion followed by work up and purification as given in section 4.7.3.3 provided 1b in 64% yield (Table 1, entry 15).

The above reaction was also conducted using 0.85 mmol (Table 1, entry 16) or 0.43 mmol (Table 1, entry 17) of piperidine, the yield of 1b was found to increase up to 69% in case when 0.85 mmol of piperidine was used.

Thus, 1.28 mmol of HCOONa and 0.85 mmol of piperidine was found to be the effective base combination and used in all the subsequent experiments.

4.7.3.6 Effect of various other ionic liquids such as [bmim]BF$_4$, [bmim]PF$_6$ and [bmim]OH or solvent DMF in place of [hmim]Br with Pd(OAc)$_2$, PPh$_3$ and HCOONa-piperidine combination (Table 2, entry 2-5):

The reactions were performed in the same manner as given in section 4.7.3.5 in [bmim]BF$_4$, [bmim]PF$_6$ and [bmim]OH replacing [hmim]Br in equal amounts (1.5 g in each case). The reactions upon completion followed by work up and column purification as given in section 4.7.3.3 provided 1b in 22, 21 and 19% yields. Also, no product formation was observed when DMF (4 ml) was used as a solvent in place of IL (Table 2, entry 5)

Thus, [hmim]Br was found to be the effective IL and used in all the subsequent experiments.

4.7.3.7 Effect of different Pd catalysts such as PdCl$_2$, Pd(PPh$_3$)$_4$, Pd(CF$_3$COO)$_2$, PdCl$_2$(PPh$_2$)$_2$ on one-pot synthesis of 1b from 1a using HCOONa-piperidine in [hmim]Br (Table 2, entries 6-9):

The reactions were performed in the same manner as given in section 4.7.3.5 with PdCl$_2$, Pd(PPh$_3$)$_4$, Pd(CF$_3$COO)$_2$ and PdCl$_2$(PPh$_3$)$_2$ replacing Pd(OAc)$_2$ in equal molar amounts in each case while no ligand (PPh$_3$) was used in the case with Pd(PPh$_3$)$_4$ and PdCl$_2$(PPh$_3$)$_2$. The above reactions upon completion followed by work up and purification as given in section 4.7.3.3 provided 1b in 71, 68, 72 and 74% yields in the case of PdCl$_2$, Pd(PPh$_3$)$_4$,
Microwave promoted tandem.....

Chapter 4

Pd(CF$_3$COO)$_2$ and PdCl$_2$(PPh$_3$)$_2$ respectively. Thus, PdCl$_2$(PPh$_3$)$_2$ was found to be the optimum catalyst and used in all the subsequent experiments.

4.7.3.8 One-pot synthesis of 1b from 1a using HCOONa-piperidine, PdCl$_2$(PPh$_3$)$_2$ in [hmim]Br with different additives such as LiCl, Ag$_2$O, Ag$_2$CO$_3$ (Table 2, entries 10-12):
The reactions were performed in the same manner as given in section 4.7.3.5 using PdCl$_2$(PPh$_3$)$_2$ as a catalyst (without PPh$_3$) along with addition of various additives such as LiCl, Ag$_2$O and Ag$_2$CO$_3$ (8 mol% in each reaction). The reactions upon completion followed by work up and purification as given in section 4.7.3.3 provided 1b in 78, 67 and 62% yields in the case of LiCl, Ag$_2$O, Ag$_2$CO$_3$ respectively. Thus, LiCl was found to be the optimum additive and used in all the subsequent experiments.

4.7.3.9 One pot synthesis of 1b from 1a using PdCl$_2$(PPh$_3$)$_2$, HCOONa-piperidine in [hmim]Br with LiCl as an additive (Table 2, entry 13) under conventional heating:
A mixture of 1-(naphthalen-2-yl)ethanol (0.22 g, 1.28 mmol), 4-idoanisole (0.2 g, 0.85 mmol), PdCl$_2$(PPh$_3$)$_2$ (4 mol%), HCOONa (1.28 mmol), piperidine (0.85 mmol) and LiCl (8 mol%) in [hmim]Br (1.5 g) was heated in an oil bath at 150°C for 14 h. The reactions upon completion followed by work up and purification as given in section 4.7.3.3 provided 1b in low yield (20%).

4.7.3.10 Optimized procedure for one pot synthesis of 1b from 1a using PdCl$_2$(PPh$_3$)$_2$, HCOONa-piperidine in [hmim]Br with LiCl as an additive (Table 3, entry 1):
A mixture of 1-(naphthalen-2-yl)ethanol (0.22 g, 1.28 mmol), 4-idoanisole (0.2 g, 0.85 mmol), PdCl$_2$(PPh$_3$)$_2$ (4 mol%), HCOONa (1.28 mmol), piperidine (0.85 mmol) and LiCl (8 mol%) in [hmim]Br (1.5 g) was irradiated under focused MW (120W, 150°C) for 15 min. After the completion of reaction (on TLC basis), water (20 ml) was added to the reaction mixture and extracted with ethyl acetate (2x25 ml). The combined organic layer was washed with water (2x10 ml), brine (1x10 ml), dried over Na$_2$SO$_4$ and vacuum evaporated. The obtained residue was subsequently purified by column chromatography on silica gel (60-120 mesh size) using 2% ethylacetate in hexane to give a white solid which was further recrystallised in methanol to provide pure 2-[(E)-2-(4-methoxyphenyl)ethenyl]naphthalene (1b, 78% yield) whose NMR spectra matched well with that obtained in section 4.7.3.3.

The above procedure was also followed for the synthesis of other stilbenes (Table 3, 2b-14b)
Microwave promoted tandem... Chapter 4

4-[(E)-2-(Naphthalen-2-yl)ethenyl]phenol (2b) [Maya et al. (2005)]

![Chemical structure](image)

White solid (77%), m.p. 205-207°C, $^1$H NMR (300 MHz, CDCl$_3$ + DMSO-$d_6$); δ (ppm) 8.67 (1H, b, s), 7.77-7.75 (4H, m), 7.70 (1H, d, $J = 8.7$ Hz), 7.45-7.38 (4H, m), 7.18 (1H, d, $J = 16.3$ Hz), 7.08 (1H, d, $J = 8.2$ Hz); $^{13}$C NMR (75.4 MHz, CDCl$_3$ + DMSO-$d_6$); δ (ppm) 157.5, 135.7, 134.1, 133.1, 129.3, 129.2, 128.5, 128.2, 128.0, 126.6, 126.2, 126.1, 125.9, 123.8 and 116.2. HRMS-ESI: m/z [M+H]$^+$ for C$_{18}$H$_{14}$O, calculated 247.1117; observed 247.1128.

2-[(E)-2-(4-Chlorophenyl)ethenyl]naphthalene (3b) [Saiyed and Bedekar (2010)]

![Chemical structure](image)

White solid (84%), m.p. 180-183°C, $^1$H NMR (300 MHz, CDCl$_3$ + DMSO-$d_6$); δ (ppm) 7.87-7.84 (4H, m), 7.76 (1H, d, $J = 8.6$ Hz), 7.52-7.45 (4H, m), 7.38 (2H, d, $J = 8.3$ Hz), 7.30 (1H, d, $J = 16.3$ Hz), 7.22 (1H, d, $J = 16.3$ Hz); $^{13}$C NMR (75.4 MHz, CDCl$_3$ + DMSO-$d_6$); δ (ppm) 136.0, 134.6, 133.8, 133.2, 129.5, 129.0, 128.6, 128.2, 128.0, 127.9, 127.8, 127.0, 126.7, 126.3 and 123.6.

3-[(E)-2-(Naphthalen-2-yl)ethenyl]pyridine (4b)

![Chemical structure](image)

Creamish solid (47%), m.p. 116-119°C, $^1$H NMR (300 MHz, CDCl$_3$); δ (ppm) 8.79 (1H, s), 8.53 (1H, d, $J = 4.2$ Hz), 7.89-7.85 (5H, m), 7.77 (1H, d, $J = 8.6$ Hz), 7.54-7.46 (2H, m), 7.37-7.28 (2H, m) and 7.22 (1H, d, $J = 16.4$ Hz); $^{13}$C NMR (75.4 MHz, CDCl$_3$); δ (ppm) 149.0, 134.5, 134.0, 133.6, 133.4, 133.0, 131.2, 128.9, 128.5, 128.1, 127.5, 126.9, 126.6, 125.5, 124.0 and 123.7. HRMS-ESI: m/z [M+H]$^+$ for C$_{17}$H$_{13}$N, calculated 232.1121; observed 232.1134.

2-[(E)-2-(4-Nitrophenyl)ethenyl]naphthalene (5b)

![Chemical structure](image)

Yellow solid (89%), m.p. 165-167°C, $^1$H NMR (300 MHz, CDCl$_3$); δ (ppm) 8.27 (2H, d, $J = 8.6$ Hz), 7.93 (1H, s), 7.90-7.84 (3H, m), 7.79 (1H, d, $J = 8.6$ Hz), 7.70 (2H, d, $J = 8.6$ Hz), 7.60-7.49 (2H, m), 7.48 (1H, d, $J = 16.3$ Hz) and 7.30 (1H, d, $J = 16.3$ Hz); $^{13}$C NMR (75.4 MHz, CDCl$_3$); δ (ppm) 147.1, 144.2, 134.0, 133.9, 133.7, 129.0,

192
Microwave promoted tandem…..

128.6, 128.3, 128.1, 127.2, 127.0, 126.9, 124.6 and 123.7. HRMS-ESI: m/z [M+H]⁺ for C₁₉H₁₃NO₂, calculated 276.1019; observed 276.1035.

**Table 3, entries 6-7, NMR same as compounds 1b and 5b respectively.**

4-[(E)-2-(6-Methoxynaphthalen-2-yl)ethenyl]phenol (8b)

White solid (75%), m.p. 223-226°C, ¹H NMR (300 MHz, CD₃COCD₃); δ (ppm) 8.56 (1H, b, s), 7.92-7.77 (4H, m), 7.51 (2H, d, J = 8.5 Hz), 7.28-7.12 (4H, m), 6.90 (2H, d, J = 8.5 Hz), 3.92 (3H, s);

¹³C NMR (75.4 MHz, CD₃COCD₃); δ (ppm) 159.6, 159.0, 135.9, 135.2, 131.0, 130.4, 129.6, 129.5, 128.9, 127.5, 127.4, 125.7, 120.6, 117.3, 107.7 and 56.5. HRMS-ESI: m/z [M+H]⁺ for C₁₉H₁₆O₂, calculated 277.1223; observed 277.1216.

1-4-{[(E)-2-(6-Methoxynaphthalen-2-yl)ethenyl]phenyl}ethanone (9b)

Pale yellow solid (76%), m.p. 203-206°C, ¹H NMR (300 MHz, CDCl₃); δ (ppm) 8.00 (2H, d, J = 8.3 Hz), 7.84-7.71 (4H, m), 7.64 (2H, d, J = 8.3 Hz), 7.41 (1H, d, J = 16.2 Hz), 7.28 (1H, d, J = 10.3 Hz), 7.19 (2H, d, J = 9.7 Hz), 3.95 (3H, s), 2.63 (3H, s);

¹³C NMR (75.4 MHz, CDCl₃); δ (ppm) 197.8, 158.5, 142.6, 136.2, 135.0, 132.5, 132.0, 130.0, 129.4, 129.3, 127.7, 127.6, 127.0, 126.7, 124.4, 119.6, 106.4, 56.7 and 26.9. HRMS-ESI: m/z [M+H]⁺ for C₂₁H₁₈O₂, calculated 303.1379; observed 303.1352.

4-[(E)-2-(Biphenyl-4-yl)ethenyl]phenol (10b)

White solid (74%), m.p. 128-131°C, ¹H NMR (300 MHz, CDCl₃ + DMSO-d₆); δ (ppm) 9.10 (1H, br, s), 7.63-7.53 (7H, m, J = 9.2 Hz), 7.46-7.33 (6H, m), 6.85 (2H, d, J = 8.5 Hz); ¹³C NMR (75.4 MHz, CDCl₃ + DMSO-d₆); δ (ppm) 156.9, 139.9, 138.9, 136.3, 128.3, 128.2, 128.0, 127.3, 126.8, 126.6, 126.2, 126.0, 124.4 and 115.3.

N-4-{[(E)-2-(Biphenyl-4-yl)ethenyl]-2-fluorophenyl}acetamide (11b)

Creamy solid (61%), m.p. 237-240.5 °C, ¹H NMR (300
Microwave promoted tandem...... Chapter 4

MHz, pyridine-$d_5$; $\delta$ (ppm) 8.66-8.60 (1H, m), 7.77-7.75 (5H, m), 7.63-7.61 (2H, m), 7.55-7.36 (6H, m), 2.37(3H, s); $^{13}$C NMR (75.4 MHz, pyridine-$d_5$); $\delta$ (ppm) 171.1, 151.7, 151.4, 142.4, 142.1, 138.4, 131.0, 130.5, 129.4, 129.3, 128.8, 125.5, 125.2, 114.8, 114.5 and 25.7.

1-{4-[(E)-2-(4-Chlorophenyl)ethenyl]phenyl}ethanone (12b)

Creamish solid (59%), m.p. 137-141°C, $^1$H NMR (300 MHz, CDCl$_3$); $\delta$ (ppm) 7.98 (2H, d, $J = 8.2$ Hz), 7.60 (2H, d, $J = 8.2$ Hz), 7.49 (2H, d, $J = 8.4$ Hz), 7.38 (2H, d, $J = 8.4$ Hz), 7.22 (1H, d, $J = 16.3$ Hz), 7.13 (1H, d, $J = 16.3$ Hz), 2.63 (3H, s); $^{13}$C NMR (75.4 MHz, CDCl$_3$); $\delta$ (ppm) 197.8, 142.0, 136.5, 135.6, 134.3, 130.4, 129.4, 129.3, 128.4, 128.3, 126.9 and 26.9. HRMS-ESI: m/z [M+H]$^+$ for C$_{16}$H$_{13}$OCl, calculated 257.0728; observed 257.0754.

1-{4-[(E)-2-(1,3-Benzodioxol-5-yl)ethenyl]phenyl}ethanone (13b)

Light yellow solid (63%), m.p. 159-161°C, $^1$H NMR (300 MHz, CDCl$_3$); $\delta$ (ppm) 7.96 (2H, d, $J = 8.3$ Hz), 7.57 (2H, d, $J = 8.3$ Hz), 7.18-7.09 (2H, m), 7.00-6.93 (2H, m), 6.84 (1H, d, $J = 8.0$ Hz), 6.00 (2H, s), 2.61 (3H, s); $^{13}$C NMR (75.4 MHz, CDCl$_3$); $\delta$ (ppm) 197.8, 148.6, 148.3, 142.5, 136.1, 131.6, 131.5, 129.2, 126.6, 126.1, 122.5, 108.9, 106.0, 101.6 and 26.9. HRMS-ESI: m/z [M+H]$^+$ for C$_{17}$H$_{14}$O$_3$, calculated 267.1016; observed 267.1030.

4-[(E)-2-(1,3-Benzodioxol-5-yl)ethenyl]benzonitrile (14b)

Creamish solid (68%), m.p. 139-140°C, $^1$H NMR (300 MHz, CDCl$_3$); $\delta$ (ppm) 7.63 (2H, d, $J = 7.6$ Hz), 7.55 (2H, d, $J = 7.7$ Hz), 7.16-7.08 (2H, m), 6.99-6.88 (2H, m), 6.84 (1H, d, $J = 8.0$ Hz), 6.01 (2H, s); $^{13}$C NMR (75.4 MHz, CDCl$_3$); $\delta$ (ppm) 148.7, 148.6, 142.3, 132.8, 132.4, 131.2, 127.0, 125.3, 122.8, 119.5, 110.5, 108.9, 106.0 and 101.7. HRMS-ESI: m/z [M+H]$^+$ for C$_{16}$H$_{11}$NO$_2$, calculated 250.0863; observed 250.0856.
4.8 References:
Microwave promoted tandem…..

Chapter 4


Microwave promoted tandem…..

Chapter 4


Microwave promoted tandem......

Chapter 4


198


Microwave promoted tandem….

Chapter 4


NMR spectra of some compounds

\begin{center}
\includegraphics[width=0.8\textwidth]{nmr_spectra}
\end{center}

$^{1}\text{H NMR (in CDCl}_3\text{) spectrum of 2-}\{(E)-(4-Methoxyphenyl)ethenyl\}\text{naphthalene (1b, Table 3)}$

$^{13}\text{C NMR (in CDCl}_3\text{) spectrum of 2-}\{(E)-2-(4-Methoxyphenyl)ethenyl\}\text{naphthalene (1b, Table 3)}$
1H NMR (in CDCl₃) spectrum of 3-[(E)-2-(Naphthalen-2-yl)ethenyl]pyridine (4b, Table 3)

13C NMR (in CDCl₃) spectrum of 3-[(E)-2-(Naphthalen-2-yl)ethenyl]pyridine (4b, Table 3)
Microwave promoted tandem…..

Chapter 4

HRMS spectrum of 3-[(E)-2-(Naphthalen-2-yl)ethenyl]pyridine (4b, Table 3)

$^1$H NMR (in CD$_3$COCD$_3$) spectrum of 4-[(E)-2-(6-Methoxynaphthalen-2-yl)ethenyl]phenol (8b, Table 3)
$^{13}$C NMR (in CD$_3$COCD$_3$) spectrum of 4-[(E)-2-(6-Methoxynaphthalen-2-yl)ethenyl]phenol (8b, Table 3)

HRMS spectrum of 4-[(E)-2-(6-Methoxynaphthalen-2-yl)ethenyl]phenol (8b, Table 3)
Microwave promoted tandem.... Chapter 4

$^1$H NMR (in CDCl$_3$) spectrum of 1-\{4-[E]-2-(1,3-Benodioxol-5-yl)ethenyl]phenyl\}ethanone (13b, Table 3)

$^{13}$C NMR (in CDCl$_3$) spectrum of 1-\{4-[E]-2-(1,3-Benodioxol-5-yl)ethenyl]phenyl\}ethanone (13b, Table 3)
HRMS spectrum of 1-\{4-\{(E)-2-(1,3-Benzodioxol-5-yl)ethenyl]phenyl\}ethanone (13b, Table 3)