General Introduction

Synthetic Studies of Some Bioactive C-Alkylated Phenolics and Heteroaromatic Compounds Using Green Methodologies

“What I cannot create, I do not understand”

……..Richard P. Feynman

I.1 Introduction

One of the finest accomplishments of contemporary scientific age is the ability to construct predefined molecular scaffolds using fundamental concepts of atomic structure and reactivity. Such techniques of “chemical synthesis” [Corey and Cheng (1989); Wender and Miller (2009)] have lead to invention of unprecedented drugs and materials while simultaneously enriching and expanding the horizons of human experience in formerly unimagined ways [Nicolaou and Montagnon (2008)]. The above pursuit of chemical synthesis has been largely inspired by nature which is not only a synthetic chemist *par excellence* but also a quintessential repository of bewildering array of structurally and functionally diverse organic compounds [Clardy and Walsh (2004)]. In fact a vast majority of currently used drugs have directly or indirectly been inspired by plant derived molecules [Harvey (2008); Ganesan (2008)]. According to some recent surveys, 36 new drugs derived from natural products were introduced in the market between 2001 and 2007 [Lam (2008); Harvey (2008); Butler (2008)]. Some representative examples of such natural products along with their bioactivities are shown in Figure 1.

![Figure 1](image_url)

Galantamine (Anti-Alzheimer's)  Mevastatin (Hypolipidimic)  Thienamycin (antibacterial)
Although, nature provides vital clues for biologically active lead candidates, however, such compounds are often present in only feeble concentration in their natural sources. In the above scenario, the synthesis of these compounds becomes indispensable to meet burgeoning global demand. Interestingly, the above limitation has frequently served as a blessing in disguise as the repertoire of synthetic organic chemistry has been substantially augmented [Nicolaou and Snyder (2004)] by addressing the challenges offered by synthesis of such natural product targets.

On the other hand, the contemporary times have placed organic synthesis at the cross roads, wherein, several fresh challenges and opportunities promise its further enrichment [Gartner et al. (2003); Li and Trost (2008)]. For instance, the deleterious environmental impact of some of the current chemical practices has prompted grave concerns regarding the very future of planet “earth” [Eissen et al. (2002); Gartner et al. (2003); Khetan and Collins (2007)]. Consequently, organic synthesis has been confronted with a radically new challenge i.e “sustainable or green chemistry”, wherein, a search for innovative solutions for reduction of chemical steps, wastes and energy has become the central objective [Anastas and Warner (1998); Li and Trost (2008); Trost (2002)]. The present study aimed to address some of the above challenges of green chemistry by focusing on few important classes of phenolic compounds like phenylethanoids, phenylpropanoids and phenylpentanoids (1,5-diphenylpenta-2,4-dien-1-ones) besides some heteroaromatic compounds.

I.2 Brief description and significance of phenolics and heteroaromatic compounds taken up in this study

I.2.1 Phenolics

The term “Phenolics” refers to the compounds having at least one aromatic ring with one or more hydroxyl group attached. These are widely dispersed in the plant kingdom, wherein, about 8000 phenolic structures have been reported [Crozier et al. (2009)]. A majority of the phenolic compounds are secondary metabolites which are synthesized by plants during normal development as well as in response to stress conditions such as infection, wounding, and UV radiation etc. [Harborne and Dey (1989); Kondratyuk and Pezzuto (2004)]. Some of the main functions of phenolics in plants includes their role as phytoalexins, antifeedants, attractants for pollinators, contributors to the plant
pigmentation, antioxidants, and protective agents against UV light [Kondratyuk and Pezzuto (2004)]. On the other hand, phenolics are also widely present in food products, wherein, these contribute to their bitterness, astringency, color, flavor, odor and oxidative stability [Naczk and Shahidi (2004)]. Overall, phenolics are a large and heterogeneous group of natural products which range from simple, low molecular weight, single aromatic-ring compounds to the large and complex tannins and derived polyphenols [Harborne and Dey (1989)]. These can be classified by distinguishing the number of carbon atoms in conjunction with the structure of basic phenolic skeleton (Table 1) [Crozier et al. (2009)].

Table 1. Classification of phenolics along with some representative examples

<table>
<thead>
<tr>
<th>Basic skeleton</th>
<th>Representative Classes</th>
<th>Basic Structure</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>C&lt;sub&gt;6&lt;/sub&gt;</td>
<td>Simple phenols</td>
<td><img src="#" alt="Basic Structure" /></td>
<td>Catechol, Resorcinol</td>
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<tr>
<td></td>
<td>Benzoquinones</td>
<td><img src="#" alt="Basic Structure" /></td>
<td>Ubiquinone</td>
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<tr>
<td>C&lt;sub&gt;6&lt;/sub&gt;-C&lt;sub&gt;1&lt;/sub&gt;</td>
<td>Phenolic acids</td>
<td><img src="#" alt="Basic Structure" /></td>
<td>p-Hydroxybenzoic acids</td>
</tr>
<tr>
<td>C&lt;sub&gt;6&lt;/sub&gt;-C&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Styrenes</td>
<td><img src="#" alt="Basic Structure" /></td>
<td>4-Vinylguaiacol, Canolol</td>
</tr>
<tr>
<td></td>
<td>Phenylacetic acids</td>
<td><img src="#" alt="Basic Structure" /></td>
<td>p-Hydroxy-phenylacetic acids</td>
</tr>
<tr>
<td>C&lt;sub&gt;6&lt;/sub&gt;-C&lt;sub&gt;3&lt;/sub&gt;</td>
<td>Phenylpropenes</td>
<td><img src="#" alt="Basic Structure" /></td>
<td>β-Asarone, Isosafrole</td>
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<td></td>
<td>Cinnamic esters</td>
<td><img src="#" alt="Basic Structure" /></td>
<td>Methylcinnamate</td>
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<tr>
<td>Compound Class</td>
<td>Chemical Structure</td>
<td>Examples</td>
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<tr>
<td>Coumarins</td>
<td><img src="image" alt="Coumarin Structure" /></td>
<td>Umbelliferone, Aesculetin</td>
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<tr>
<td>α-phenylpropionaldehydes</td>
<td><img src="image" alt="Aldehyde Structure" /></td>
<td>Hydrotropaldehyde</td>
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<tr>
<td>Naphthaquinones</td>
<td><img src="image" alt="Naphthaquinone Structure" /></td>
<td>Juglone</td>
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<tr>
<td>Xanthones</td>
<td><img src="image" alt="Xanthone Structure" /></td>
<td>Mangostin, Mangiferin</td>
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<tr>
<td>Stilbenes</td>
<td><img src="image" alt="Stilbene Structure" /></td>
<td>Resveratrol, Combretastatin</td>
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<td>Anthraquinones</td>
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<td>Emodin</td>
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<tr>
<td>Chalcones</td>
<td><img src="image" alt="Chalcone Structure" /></td>
<td>Phloridzin, Chalconaringenin</td>
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<td>Flavones</td>
<td><img src="image" alt="Flavone Structure" /></td>
<td>Sinensetin, Nobiletin</td>
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<td>Flavonols</td>
<td><img src="image" alt="Flavonol Structure" /></td>
<td>Quercetin, Kaempferol</td>
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<tr>
<td>Flavanols</td>
<td><img src="image" alt="Flavanol Structure" /></td>
<td>Catechin, Epicatechin</td>
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</table>
It is evident from Table 1 that phenolic compounds may also bear alkyl side chains to their core aromatic structure. In fact, a number of abundantly available bioactive phenolics possess two to three carbon side chain and are termed as phenylethanoids and phenyl propanoids respectively [Dixon and Paiva (1995)]. Further, the functional groups such as -COOH, -CHO, -C=C-, halogen, NH$_2$ and NO$_2$ etc. may be attached either to phenyl ring or to the side alkyl chain.

I.2.1.1 Biosynthetic origin of phenolics (phenylethanoids and phenylpropanoids)

A majority of the phenylethanoids and phenylpropanoids present in nature are produced by the phenylpropanoid pathway or its combination with polyketide pathway. The starting molecule of this pathway is the amino acid phenylalanine which is in turn synthesized by the shikimate pathway. In the first step (Figure 2), phenylalanine undergoes deamination into trans-cinnamic acid which is catalyzed by phenylalanine deaminase.

![Figure 2](image-url)  
*Figure 2.* An overview of the biosynthetic relationship between some common phenylethanoids and phenylpropanoids.
ammonia lyase (PAL). Subsequently, this trans-cinnamic acid undergoes hydroxylation followed by formation of 4-coumaryl-CoA. The 4-coumaryl-CoA is one of the most important molecules in this pathway as it serves as a precursor to a majority of the phenylpropanoid as well as the phenylethanoids. Thus a series of reactions like methylation, decarboxylation and reduction etc. gives rise to diverse scaffolds like styrenes, cinnamaldehydes, phenylpropenes etc. On the other hand, 4-coumaryl-CoA also enters another biosynthetic pathway i.e the polyketide pathway, wherein, enzymes like chalcone synthase (CHS) and stilbene synthase (STS) catalyze the formation of a linear tetraketide intermediate. Subsequently, CHS cyclizes this intermediate by an intramolecular Claisen condensation into a chalcone, while STS uses a different cyclization mechanism, involving an aldol condensation, accompanied by an additional decarboxylation leading to the formation of a hydroxy stilbene.

A brief description of some of the phenolic compounds taken up in the present study is given below:

I.2.1.2 Phenylethanoids: Styrenes and Stilbenes
The term “phenylethanoids” denotes organic compounds possessing C<sub>6</sub>-C<sub>2</sub> skeleton. Amongst the various phenylethanoids, this study is focused on two important classes viz. styrenes and stilbenes.

I.2.1.2.1 Styrenes
The simplest class of phenylethanoids is the styrenes which possesses a vinylene substituted aromatic ring (Figure 3).

- **Significance of Styrenes**

  *Bioactive and Flavoring agents*

Styrenes are a highly useful class of compounds having wide ranging industrial, medicinal and synthetic applications. In particular, the 4-hydroxy substituted styrenes (4-vinylphenols) are widely distributed in the plants and these are responsible for fragrance and flavor of various phenolic natural products [Crouzet et al. (1997); Nagashima et al. (1999)]. For instance, 4-hydroxy-3-methoxystyrene (4-vinylguaiacol, (VG), Figure 4a)
occurs naturally in fruits of feijoa and strawberry, raw asparagus etc [Crouzet et al. (1997)]. VG is one of the most important and FEMA GRAS (Flavour and Extract Manufacturers Association Generally Regarded As Safe) approved flavoring agent in food and pharmaceutical industry. On the other hand, canolol, (Figure 4b) a natural 4-vinylphenol occurring in rapeseed oil has been found to display potent antioxidant [(Kuwahara et al. (2004)] and anticancer activities [Cao et al. (2007)].

**Synthons in organic chemistry**

One of the most significant application of styrenes in organic synthesis lies in their use for production of fine chemicals through transition metal catalysis. For instance, the venerable hydroformylation reaction utilizes styrene as one of the primary feedstocks for synthesis of carbonyl compounds which in turn find wide ranging industrial applications (Scheme 1), [Kohlpaintner and Frohning (1996)].

![Scheme 1](image)

Similarly, the classical Heck reaction comprises a transition metal (Pd) catalyzed coupling of styrenes with arylhalides [Beletskaya and Cheprakov (2000)]. This transformation is a prominent route towards synthesis of biologically active compounds like stilbenes etc. (Scheme 2).

![Scheme 2](image)
Another important application of styrenes involves their use as precursors for polystyrenes and a host of other copolymers like styrene-butadiene rubber (SBR), styrene-divinylbenzene (S-DVB) and unsaturated polyesters etc. [Hirao et al. (2002); Scheirs and Priddy (2003)]. These polymeric compounds are important components of materials such as rubber, plastic insulation, fiberglass and automobile parts etc.

I.2.1.2.2 Stilbenoids

The stilbene moiety can be considered to arise from a core C$_6$-C$_2$ skeleton by replacement of H atom from side chain with a C$_8$H$_5$ moiety (Figure 5a). Similarly, the substitution of a H atom from one of the aryl rings of stilbene with a phenylenevinylene (PV) group provides the distyrylbenzene (Figure 5b) which are the simplest members of oligophenylenevinylene (OPV, Figure 5c). In this study, the term stilbenoids would be used to denote both the simplest stilbene scaffolds as well as their derivatives like oligophenylenevinylene (OPV).

![Figure 5](image.png)

- **Significance of stilbenes**

Stilbenes have been the subject of considerable research activities as these possess numerous implications in plant disease resistance and human health [Chong et al. (2009); Likhtenshtein (2009)]. In nature, a majority of the stilbenes occur in their hydroxylated forms. These scaffolds are vital components of plant defense against attack by pathogens and hence are often referred to as phytoalexins (plant antibiotics). Moreover, a number of naturally occurring hydroxy stilbenes [Shen et al. (2009)] are vital lead agents in the medicinal chemistry domains [Roupe et al. (2006)]. One of the most well known hydroxystilbenes is resveratrol (trans-3,5,4′-trihydroxy stilbene, Figure 6) which occurs in...
fruits such as red grapes and mulberry etc. [Shen et al. (2009)]. The significant interest generated by resveratrol arises from its remarkable pharmacological properties, wherein, a number of studies have implicated it to be an effective cardio-protective and cancer preventive agent [Jang et al. (1997); Baur and Sinclair (2006); Delmas et al. (2006)]. In fact, the cholesterol lowering properties of resveratrol have spurred its linkage to the so called “French paradox”, wherein, low incidence of coronary heart disease amongst the french despite their high fat diets has been linked to their consumption of red wine [Renaud and Lorgeril (1992); Iriti and Faoro (2006)].

Another pharmacologically important hydroxy stilbene is combretastatin which was first isolated from the bark of *Combretum caffrum* (african bush willow tree) [Pettit et al. (1982); Pettit et al. (1989)]. The various members of combretastatin family possess varying ability to cause vascular disruption in tumors [Lin et al. (1989)]. Amongst these, combretastatin A-4 (Figure 6) is one of the most potent anticancer agents [Pettit and Rhodes (1998); Nam et al. (2003); Hori and Saito (2003)] owing to its strong tubulin binding ability and cytotoxicity [Hori and Saito (2003)]. Moreover, the phosphate prodrugs of combretastatin A-4 are currently in clinical trials for treatment of anaplastic thyroid cancer against which there is currently no FDA approved treatment [Cooney et al. (2005)]. Similarly, a number of other natural hydroxy stilbenes like pterostilbene (Figure 6), piceatannol and viniferins etc. [Shen et al. (2009)] also possess significant pharmacological activities [Manickam et al. (1997); Roupe et al. (2006)].

- **Significance of oligophenylenevinylenes**

The term *oligophenylenevinylene* (OPV) refers to short chains of pi conjugated molecules containing repeated phenylene-vinylene (PV) units

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**Figure 6.** Some biologically active hydroxy stilbenes

**Figure 7**
(Figure 7) [Meir (2006)]. Thus, the OPV’s with n=1 represents the stilbene moiety, while, oligomers with n=2, 3 etc are respectively termed as distyrylbenzenes and tristyrylbenzenes etc (Figure 8).

![Figure 8. Some representative OPV’s with varying degrees of oligomerization and topology](image)

These molecules possess profound applications in fields as diverse as optoelectronics, material science, supramolecular chemistry and medicinal chemistry [Mullen and Wegner (1998); Meir (2006)]. For instance, the unique mechanical and electronic properties of OPV’s make them attractive materials for devices such as organic light emitting diodes (OLED’s) [Goodson et al. (1997); Hulvat et al. (2005)].

On the other hand, the functionalized short chains of OPV’s like distyrylbenzene show potent binding ability to amyloid (Aβ) fibrils [Skovronsky et al. (2000)]. The accumulation of such Aβ plaques in the brain cells is a characteristic feature of neurodegenerative disorders like Alzheimer’s disease (AD) [Hardy and Selkoe (2002)]. Consequently, the amyloid (Aβ) fibril binding ability of distyrylbenzenes coupled with their remarkable optical properties renders them one of the most promising agents for management of AD [Schmidt et al. (2001)].
1.2.1.3 Phenylpropanoids: *Phenylpropenes, α-phenylpropionaldehydes and cinnamic esters*

The phenylpropanoids are the compounds possessing one or more C₆-C₃ skeleton [Dixon and Paiva (1995)]. They play vital roles in the interaction of plants with their surrounding environment and mediate the plant response to biotic and abiotic stress [Dixon and Paiva (1995); Vogt (2010)]. The phenylpropanoids represent the largest pool of secondary metabolites, comprising nearly 20% of total carbon in the terrestrial biosphere [Peters (2007)], with plants synthesizing approximately 10 gigatonnes (10 x 10⁹ tonnes of carbon) of these molecules each year. Thus, this is a large family and includes several important classes of compounds such as phenylpropenes, α-arylaldehydes, propiophenones, cinnamaldehydes, cinnamic esters/acid, coumarins etc. Amongst the above, the present study is mainly concerned with phenylpropenes, α-arylaldehydes and cinnamic esters.

### 1.2.1.3.1 Phenylpropenes

Phenylpropenes are compounds having a phenyl ring and a three carbon side chain with at least one double bond (Figure 9). These are one of the major components of plant derived essential oils and constitute the second largest group of plant volatiles after terpenoids [Parmar et al. (1997); Springob and Kutchan (2009)].

![Figure 9. Some naturally occurring phenylpropenes](image)

- **Significance of Phenylpropenes**

  **Flavoring agents**

  The various natural phenylalkenes primarily function as attractants of pollinators and seed dispersals or as defense compounds in plants. In human cultures, the high flavor and
fragrant attributes of phenylpropenes has led to their use as condiments and herbal remedies since ancient times [Gang et al. (2001); Springob and Kutchan (2009)].

**Synthons in organic chemistry**

One of the major synthetic utilities of phenylpropenes lies in their use as abundantly available hydrocarbon feedstocks for synthesis of value added compounds. The peculiar presence of benzylic double bond allows their easy functionalization into a wide array of biologically and industrially important compounds (Figure 10) [Joshi et al. (2005); Joshi et al. (2006); Sinha et al. (2009)].

![Figure 10](image)

**Figure 10.** Synthetic utility of various naturally occurring phenylpropenes for synthesis of value added compounds

### I.2.1.3.2 α-phenylpropionaldehydes

The α-phenylpropionaldehydes possess a chiral benzylic position which is substituted by both aldehyde (-CHO) and alkyl/phenyl groups (Figure 11).

- **Significance of α-phenylpropionaldehydes**

The simplest α-phenylpropionaldehydes i.e hydrotropoldehyde (α-phenylpropionaldehyde), an important flavoring agent, is found in sesame seeds and finds extensive applications in
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blossom compositions [Bauer et al. (2007)]. On the other hand, the various substituted α-phenylpropionaldehydes are vital intermediates for synthesis of bioactive compounds including drugs and unnatural amino acids etc [Botteghi et al. (1991); Watkins et al. (2008); Vogt et al. (2007)]. For instance, the profen class of nonsteroidal anti-inflammatory drugs like Ibuprofen ((S)2-(4-isobutylphenyl)propionic acid) can be synthesized among others by oxidation of corresponding α-phenylpropionaldehydes ((S)2-(4-isobutylphenyl)propionaldehyde) (Scheme 3) [Barner and Kurland (1998)].

\[ \text{CHO} \quad \text{[O]} \quad \text{COOH} \]

Scheme 3

I.2.1.3.3 Cinnamic esters

The cinnamic esters represent another important class of phenylpropanoids [Harborne and Baxter (1993)] as described below:

- **Significance of Cinnamic esters**

Methyl cinnamate (Figure 12) is naturally found in a variety of plants like strawberry, sichuan pepper, *Eucalyptus olida* etc [Burdock and Fenaroli (2005)]. It is used in the flavor and perfume industries. The flavor is fruity, strawberry-like; and the odor is sweet.

\[ \text{OCH}_3 \quad \text{OCH}_2\text{CH}_3 \]

**Figure 12.** Some naturally occurring (E)-cinnamic esters

balsamic. Similarly, ethyl cinnamate is present in the essential oil of cinnamon. It has fruity and balsamic odor, reminiscent of cinnamon with an amber note [Budavari (2001)]. The \( p \)-methoxy ethyl cinnamate is reported to be a monoamine oxidase inhibitor (Figure 12) [Noro et al. (1983)]. On the other hand, 2-ethylhexyl 4-methoxycinnamate (Figure 12) is
used as a light protection filter for ultraviolet light of the wavelength range from 280-315 nm (UV-B) [Kuhn et al. (2003)].

Apart from the phenylethanoids and phenylpropanoids, this study also involves the synthetic studies of some related classes like phenyl 1,5-diphenylpenta-2,4-dien-1-ones (phenylpentanoids) besides certain aromatic/heteroaromatic compounds like nitro/chloro substituted benzenes, indoles, indazoles, quinolines etc.

I.2.1.4 1,5-diphenylpenta-2,4-dien-1-ones (Phenylpentanoids)

The 1,5-diphenylpenta-2,4-dien-1-ones are characterized by a C₆-C₅-C₆ skeleton (Figure 13). These compounds can also be considered to belong to phenolics family due to its similarity with core structures of phenylethanoids and phenylpropanoids. These compounds are attractive materials for optoelectronic applications due to the presence of extended conjugation [Ruzie et al. (2009)]. Moreover, these have also been extensively explored for biological activities [Yayli et al. (2005)] due to their close resemblance with well known pharmacophores like chalcones [Youssef et al. (2007)].

I.2.2 Heteroaromatic compounds

Aromatic compounds which contain heteroatoms (e.g. O, N, S) as part of the cyclic conjugated π-system are called heteroaromatic compounds. Some of the N-heteroaromatic compounds are represented by the indoles, indazoles, quinolines etc. (Figure 14). These nitrogen containing compounds comprise the core structures of various bioactive compounds [Gibson et al. (1996)]. For instance, indole possesses a bicyclic structure consisting of a six membered benzene ring fused to a five membered nitrogen containing pyrrole ring (Figure 14). It is an important structural component of numerous pharmaceutical agents [Horton et al. (2003); Wood et al. (2009)]. Similarly, the various other N-heteroaromatic compounds such as indazoles, quinolines etc. (Figure 14) also possess profound applications in pharmaceutical and agrochemical domains [Cerecetto et al. (2005); Lilienkampf et al. (2009)].
I.3 Current Challenges in synthesis of phenolics and heteroaromatic compounds

Though many of the above discussed phenolic and heteroaromatic compounds are present in natural sources, however, their feeble concentrations are not sufficient to meet the increasing global demand. In this context, the semi-synthetic/synthetic approaches assume importance as these also provide the flexibility to install any of the desired functionalities on such scaffolds.

In view of their immense importance, various synthetic approaches have been reported for the above mentioned phenolic and heteroaromatic compounds. Although some of these methodologies are beneficial in their own right, however, a majority of the prevalent protocols continue to be afflicted with challenges like multistep protocols, use of harsh reagents etc., thereby, rendering these approaches to be unsustainable in view of the heightened environmental concerns.

In order to ameliorate the above limitations, it becomes imperative to employ new paradigms of organic synthesis. In this context, the concepts and tools of green chemistry offer a platform, wherein, hitherto unfathomable opportunities can be readily discovered.

I.4 Green Chemistry

The twentieth century witnessed a phenomenal impact of chemical industry on societal development as chemistry was perceived as a solution to a host of society’s needs [Levere (2001); Nicolaou and Montagnon (2008)]. However, in recent times the above perception of chemical industry has undergone a dramatic reversal while the deleterious ecological impact of above chemical technologies has started to emerge [Eissen et al. (2002); Gartner et al. (2003); Khetan and Collins (2007)]. Thus, the global community is confronted with such grave perils like ozone depletion and environment change which has literally threatened the future of human race [Eissen et al. (2002); Colborn et al. (1996)].
principal factors responsible for above scenario include the indiscriminate use of non-renewable resources, generation of hazardous chemical waste besides use of energy-intensive processes etc. To quote just one instance, about 7.1 billion pounds of more than 650 toxic chemicals were released to the environment by the United States alone [Doble et al. (2007)].

In the above backdrop, the concept of “Green chemistry” assumes paramount importance as it seeks to provide a platform for sustainable chemical practices [Anastas and Werner (1998)]. In the simplest of terms, green chemistry is the “design of chemical products and processes that reduce or eliminate the use and generation of hazardous substances”. It also includes use of sustainable raw materials and energy resources for manufacturing process. In other words, green and sustainable chemistry aims to develop processes and technologies which lead to more efficient chemical reactions besides generating little waste and fewer environmental emissions as compared to the current chemical practices [Anastas and Werner (1998)].

The essential features of the concept of green chemistry have been enunciated in the form of a set of twelve principles [Anastas and Werner (1998)] which are mentioned below:

1. It is better to prevent waste than to treat or clean up waste after it has been created.
2. Synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product.
3. Wherever practicable, synthetic methods should be designed to use and generate substances that possess little or no toxicity to human health and the environment.
4. Chemical products should be designed to preserve efficacy of function while reducing toxicity.
5. The use of auxiliary substances (e.g., solvents, separation agents, etc.) should be made unnecessary wherever possible and innocuous when used.
6. Energy requirements should be recognized for their environmental and economic impacts and should be minimized. Synthetic methods should be conducted at ambient temperature and pressure.
7. A raw material or feedstock should be renewable rather than depleting whenever technically and economically practicable.
8. Unnecessary derivatization (use of blocking groups, protection/deprotection, temporary modification of physical/chemical processes) should be minimized or avoided if possible, because such steps require additional reagents and can generate waste.

9. Catalytic reagents (as selective as possible) are superior to stoichiometric reagents.

10. Chemical products should be designed so that at the end of their function they break down into innocuous degradation products and do not persist in the environment.

11. Analytical methodologies need to be further developed to allow for real-time, in-process monitoring and control prior to the formation of hazardous substances.

12. Substances and the form of a substance used in a chemical process should be chosen to minimize the potential for chemical accidents, including releases, explosions, and fires.

The above principles can be incorporated into any chemical process by using some enabling tools. In this context, the present studies especially involve the application of the following tools of green chemistry:

- **Multicomponent domino reactions**
- **Ionic liquids**
- **Water as solvent**
- **Innocuous and abundantly available starting materials**
- **Microwave assisted organic synthesis**

### I.4.1 Multicomponent domino reactions

One of the most common strategies for synthesis of organic compounds involves the stepwise formation of individual bonds in the targeted molecule. Evidently, such a multistep approach would generate considerable waste due to use of large amounts of solvents, reagents and energy etc. In contrast it would be more beneficial if a single operational sequence could be developed to afford the formation of several bonds without isolation of reaction intermediates and addition of reagents. Such transformations are usually termed as *domino reactions*, a concept pioneered by the German chemist Lutz F Tietze [Tietze (1996)]. As defined by Tietze, “a domino reaction is a process involving two
or more bond-forming transformations (usually C-C bonds) which take place under the same reaction conditions without adding additional reagents and catalysts, and in which the subsequent reactions result as a consequence of the functionality formed in the previous step.” The quality and importance of a domino reaction can be correlated to the number of bonds generated and the increase of complexity in such a process. They can be performed as single-, two- and multicomponent transformations [Thirumurugan et al. (2009)]. Thus, most of the known multicomponent processes but not all, can be defined as a subgroup of domino reactions [Tietze and Rackelmann (2004)].

Though the concept of domino reactions has gained recognition quite recently, however, nature has already developed several domino reaction pathways for synthesis of complex natural products. For instance, the biosynthesis of lanosterol, a steroid, proceeds through the enzymatic cyclization of (S)-2,3-oxidosqualene via opening of an epoxide followed by formation of four new bonds and simultaneous introduction of six stereocentres (Scheme 4) [Wendt et al. (2000)].

![Scheme 4. Biosynthesis of lanosterol through a domino sequence](image)

I.4.1.1 Classification of domino reactions

The domino reactions have been classified according to the mechanism of the single steps which may be of the same or of different types and which can include cationic, anionic, radical, pericyclic, transition metal-catalyzed, or redox transformations [Tietze (1996)]. Thus, the following two general classes of domino reactions are possible:

- **Homo-domino reactions**: a combination of reactions of the same mechanism
- **Hetero-domino reactions**: a sequence of reactions with different mechanisms

A majority of the domino transformations described in the literature belong to the first category i.e homo-domino reactions such as cationic-cationic, anionic-anionic, radical-radical, pericyclic-pericyclic and transition metal catalyzed reactions. In comparison to the
homo-domino reactions, the hetero-domino transformations are relatively more difficult to accomplish [Tietze (1996)]. Nevertheless, the few known hetero-domino reactions comprise one of the most powerful strategies in synthesis of architecturally complex molecules. In this context, one of the most well known heterodino sequence is the domino Knoevelengal-HeteroDiels-Alder reaction whose two component variant (Scheme 5) involves treatment of a 1,3-dicarbonyl compound with an aldehyde containing a dienophile moiety. Such a transformation has been used for a facile access towards novel and highly unusual heterocyclic scaffolds (Scheme 5) [Tietze (1996)].

**Scheme 5**

1.4.1.2 Some of the other representative examples of domino transformations are given below:

A one-pot synthesis of medicinally important 3-(diaryl)methylene)indolinones from readily available starting materials was made possible via a three component reaction between N-(4-methoxyphenyl)-N-methyl propiolamide, phenyliodide and 2-nitrophenyliodide (Scheme 6) [Pinto et al. (2007)]. The reaction employed a domino Sonagashira/Carbopalladation/C-H Activation/C-C bond forming sequence which was promoted by a single catalyst system.

**Scheme 6**
Similarly, a domino sequence involving sequential iminium-iminium-enamine catalysis enabled the consecutive formation of three new C-C bonds through reaction of $\alpha,\beta$-unsaturated aldehydes with active methylene compounds using (S)-2-[bis(3,5-bistrifluoromethylphenyl)-trimethylsilyloxy]methyl]pyrrolidine as an organocatalyst (Scheme 7) [Carlone et al. (2007)]. The methodology provided a direct access towards highly enantiopure cyclohexene derivatives.

\[
\begin{align*}
\text{O} & \quad \text{Et} \quad + \quad \text{NC} & \quad \text{CN} \\
\text{Et} & \quad \text{Et} \quad \text{Et} & \quad \text{O} \\
\text{Ar} & \quad \text{Ar} \quad \text{Ar} & \quad \text{Ar} = 3,5-(\text{CF}_3)_2\text{C}_6\text{H}_3 \\
10 \text{ mol}\% & \quad \text{PhCOOH (10 mol\%)} & \quad \text{toluene} \\
\text{Me} & \quad \text{Br} & \quad \text{Me} \quad \text{Br} & \quad \text{Me} \quad \text{Br} \\
\text{Pd(OAc)}_2 & \quad \text{tri-(2-furyl)phosphine} & \quad \text{Cs}_2\text{CO}_3, \text{CH}_3\text{CN} & \quad 90^\circ\text{C}, 24\text{h} \\
\text{75\% yield} & \quad \text{p} & \quad \text{p} & \quad \text{p} \\
\text{Scheme 7}
\end{align*}
\]

In another instance, a Pd catalyzed multicomponent domino process allowed a direct access to highly complex tetrasubstituted helical alkenes (Scheme 8) [Gericke et al. (2009)]. This domino reaction involved formation of four carbon-carbon bonds in a single operational step.

\[
\begin{align*}
\text{Me} & \quad \text{I} \quad + \quad \text{Ph} & \quad \text{Br} \\
\text{Br} & \quad \text{Br} \quad \text{Br} & \quad \text{Br} \\
\text{Ph} & \quad \text{Ph} \quad \text{Ph} & \quad \text{Ph} \\
\text{Pd(OAc)}_2 & \quad \text{tri-(2-furyl)phosphine} & \quad \text{Cs}_2\text{CO}_3, \text{CH}_3\text{CN} & \quad 90^\circ\text{C}, 24\text{h} \\
\text{75\% yield} & \quad \text{p} & \quad \text{p} & \quad \text{p} \\
\text{Scheme 8}
\end{align*}
\]

I.4.2 Unconventional solvents

Solvents are one of the auxiliary materials used in chemical synthesis. They are not an integral part of the compounds undergoing reaction, yet they play an important role in chemical production and synthesis. By far, the largest amount of “auxiliary waste” in most chemical productions is associated with solvent usage [Sheldon (2005)]. For instance, a study by GlaxoSmithKline showed that about 85% of the total mass of chemicals involved in manufacture of pharmaceuticals comprises solvents, while recovery efficiencies are
typically 50–80% [Constable et al. (2002)]. The primary function of solvents in classical chemical syntheses is to facilitate mass transfer to modulate chemical reactions in terms of reaction rate, yields, conversions, and selectivity. In addition, solvents are also extensively used for dissolving reactants, extracting and washing products, separating mixtures etc. Consequently, one of the most critical objectives of sustainable chemistry in the present scenario is the exploration of safer reaction media [Sheldon (2005)], wherein, ionic liquids and water offer the one of the most promising avenues.

I.4.2.1 Ionic Liquids

The term “Ionic Liquids” refers to salts of organic cations and inorganic anions which melt at or below 100°C [Welton (1999)]. Thus these are quite distinct from molten salts which possess high melting points. A majority of the reported ionic liquids comprise imidazolium or pyridinium moieties as cations while anions range from simple halides to tetrafluoroborates, hexfluorophosphates, triflate, tosylates etc (Figure 15) [Chowdhury et al. (2007)].

![Figure 15](image)

Figure 15. Structures and abbreviations of some commonly occurring cations and anions in ionic liquid

The earliest application of ionic liquids dates back to 1948 when chloroaluminate salts were used as bath solution for electroplating aluminium [Wasserscheid and Keim (2000)]. On the other hand, one of the first reports describing ionic liquids as new reaction media/catalysts for organic synthesis involved the use of chloroaluminate ionic liquids for promoting Friedel Crafts reaction [Wasserscheid and Keim (2000)]. Later on, a diverse array of other
organic reactions has been also found to be promoted by ionic liquids [Wasserscheid and Welton (2008)].

The major attractive features of ionic liquids *vis à vis* traditional organic solvents include

- Negligible vapor pressure
- High thermal stability
- Ability to catalyze organic reactions
- Can solublize a wide variety of organic as well as inorganic compounds
- Possibility of altering physico-chemical properties by judicious selection of cation and anion (*designer solvents*)
- Possibility of catalyst immobilization and recycling

The use of ionic liquids realizes one of the important tenants of green chemistry i.e. reduction in hazards as well as waste [Welton (1999); Wasserscheid and Welton (2008)]. This is because the negligible vapor pressure of ionic liquids ensures minimal loss of solvent to the environment which is not the case with non volatile organic solvents. Moreover, the peculiar solubility characteristics of an ionic reaction medium often allow easy recovery and reusability of catalyst [Wasserscheid and Keim (2000)]. In addition to their use as reaction media, ionic liquids have also been found to promote organic reactions thereby eliminating the need of any acid/base catalysts [Parvulescu and Hardacre (2007); Wasserscheid and Welton (2008)].

Recently, the synthetic utility of ionic liquids has been expanded through the development of chiral ionic liquids (Figure 16) [Luo et al. (2006)]. Such ionic liquids usually comprise a chiral cation which is designed from precursors such as amino acids, amino alcohols, hydroxy acids, amines and alkaloids etc [Ding and Armstrong (2005)].

**I.4.2.1.1 Some representative examples showing the synthetic applications of ionic liquids**

The ability to control the nature of product of a given reaction by just changing the *composition* of an ionic liquid represents a new paradigm in organic synthesis. Such a
“designer solvent” property of ionic liquids has been emphatically demonstrated, wherein, the reaction of toluene and nitric acid in three different ionic liquids viz. [bmim][OTf], [bmim][NO₃] and [bmim][OMs] (Scheme 9) [Earle et al. (2004)] afforded respectively three different reaction pathways i.e nitration, halogenation and oxidation.

![Scheme 9](image1)

On the other hand, ionic liquids have also been shown to be capable of replacing harsh acids/bases. In one instance, Ranu et al. found the task specific ionic liquid [bmim][OH] to be an efficient catalyst cum solvent for Michael addition of active methylene compounds to conjugated alkenes (Scheme 10) [Ranu and Banerjee (2005)].

![Scheme 10](image2)

In another instance, a dramatic rate acceleration of KF induced nucleophilic fluorination of halo/mesyl alkanes has been observed using ionic liquid [bmim] [BF₄] (Scheme 11) [Kim et al. (2002)]. The ionic liquid not only enhanced the reactivity of KF but also reduced the formation of side products.

![Scheme 11](image3)
Ionic liquids have also been found to promote asymmetric reaction. Thus, Luo et al. showed that pyrrolidine type chiral ionic liquids can efficiently catalyze enantioselective Michael additions to nitro olefins (Scheme 12) [Luo et al. (2006)]. Moreover, the above chiral ionic liquid could also be readily recycled and reused.

![Scheme 12](image)

**Scheme 12**

**I.4.2.2 Water as solvent**

Amongst the various known solvents, water assumes prime importance due to its several unmatched benefits [Li and Chen (2006); Chanda and Fokin (2007); Dallinger and Kappe (2007)]. The only natural solvent on earth is water. Moreover, it is inarguably the safest, most economical and readily available solvent. In addition, water also possesses some unique physical properties like inflammability, a large temperature window in which it remains in the liquid state, extensive hydrogen bonding, high heat capacity and large dielectric constant etc. [Chanda and Fokin (2007)]. Furthermore, the low solubility of oxygen gas in water, an important property in the early development of life in an anaerobic environment, can facilitate air-sensitive transition-metal catalysis in open air [Li (2002)]. The use of water as a solvent also implies the elimination of tedious protection–deprotection processes for certain acidic-hydrogen containing functional groups, which contributes to the overall synthetic efficiency [Li and Trost (2008)].

Despite the above positive attributes of water as solvent, organic synthesis in water at first appears counterintuitive primarily due to the extremely low solubility of most organic compounds in water. However, the low solubility of organic substrates in water can often be overcome using ionic derivatization, surfactants and hydrophilic auxiliaries etc. Surprisingly, a number of organic reactions have been found to be accelerated in water as compared to organic solvents. In many cases the above rate enhancement has been ascribed...
to a so called “hydrophobic effect” [Rideout and Breslow (1980); Rideout et al. (1983); Lindstrm and Andersson (2003)] wherein, the selectivity of an organic reaction in water is markedly affected through interaction of nonpolar or hydrophobic regions of reactants. These forces are usually too weak to compete with any steric and electronic effects in organic solvents. In water, on the other hand, hydrophobic surfaces associate strongly as a result of the tendency of water to exclude nonpolar species and thus minimize the Gibbs energy of solvation, thereby leading to the phenomenon of hydrophobic effect [Dallinger and Kappe (2007)].

I.4.2.2.1 A brief discussion of some of the prominent pathways involved in water assisted activation of organic reactions is presented below:

Some of the most path breaking studies regarding acceleration of organic reactions in water were conducted by Breslow and coworkers [Rideout and Breslow (1980); Rideout et al. (1983)] wherein, they observed the extraordinary rate enhancing effect of water as solvent on the Diels-Alder reaction of cyclopentadiene with butenone. Interestingly, above reaction was accelerated more than 700-fold in water as compared to the aprotic nonpolar organic solvent, 2,2,4-trimethylpentane (Scheme 13). The observed rate increase in water was rationalized by the hydrophobic effect, i.e. the propensity of hydrophobic molecules to associate in order to minimize their contact surface with water. Moreover, use of water led to much higher endoselectivity of cycloaddition than in ethanol or in the absence of a solvent (Scheme 13) [Rideout et al. (1983)].

![Scheme 13](image)

One of the most important strategies for reaction of water insoluble substrates involves the use of surfactants which either solublize organic materials or form their colloidal dispersions in water. In a representative case, a three component Mannich reaction of
Synthetic Studies of aldehydes, amines and ketones was developed in water using DBSA (Dodecylbenzenesulfonic acid) which acts as both an acid catalyst to activate a substrate and as a surfactant to form colloidal dispersion of water immiscible reactants [Manabe and Kobayashi (1999)]. The colloidal formation was found to play a critical role in acceleration of above reaction as the same transformation proceeded only sluggishly in organic solvents (Scheme 14).

```
\[ \text{C}_6\text{H}_5\text{CHO} + \text{C}_6\text{H}_5\text{NH}_2 + \text{dodecylbenzenesulfonic acid (10 mol\%)} \rightarrow \text{C}_6\text{H}_5\text{C}=\text{O} \text{C}_6\text{H}_5 \]
\[ \text{in H}_2\text{O: upto 69\% yield in MeOH or CH}_2\text{Cl}_2: < 10\% yield \]
```

**Scheme 14**

In a sharp contrast to above approach, the insoluble nature of organic substrates in water has itself been found to dramatically enhance the reaction rate in some cases. For instance, Turner et al. found that neat water provided an effective metal-free system for direct arylation of thiazoles (Scheme 15) [Turner et al. (2007)]. The rate acceleration in such transformations (also termed as “on water reactions” [Klijn and Engberts (2005)]) has been attributed to a substantial increase in effective concentration of reactants and catalyst systems in the heterogeneous aqueous suspensions.

```
\[ \text{ICl} + \text{SNPh}^+ + \text{H}_2\text{O, 24 h} \rightarrow \text{[Pd(dpff)Cl}_2]\text{CH}_2\text{Cl}_2 \text{PPh}_3, \text{Ag}_2\text{CO}_3, 60^\circ\text{C} \rightarrow \text{Cl} \text{SPh} \text{Cl} \]
```

**Scheme 15**

Another route for reaction rate acceleration in water involves pre-activation of catalyst. Thus, water has been found to promote the formation of a highly active Pd (0) catalyst from biaryl dialkyl phosphine mediated reduction of Pd (II) [Fors et al. (2008)]. The above catalyst system exhibited excellent efficiency in coupling of amides and anilines with acid chlorides (Scheme 16).
I.4.3 Use of readily available starting materials

The nature of the starting material of a given reaction is often a critical factor in determining its economical and ecological efficiency. Ideally, a chemical synthesis should utilize readily available or more preferably renewable source of starting materials [Bjørsvik and Liguori (2002); Meier et al. (2007)]. The use of highly functionalized reactants not only renders the chemical process on the whole to be less efficient but the high reactivity of such substrates can also make their handling to be tedious.

On the other hand, the use of abundantly available plant derived raw materials as synthons is highly advantageous as these often provide convenient templates to efficiently build up a wide array of high valued scaffolds. For instance, dihydrotagetone (2,6-Dimethyl-7-octen-4-one) is an abundantly available terpenoid isolated from several plants including Tagetes minuta [Baser and Malyer (1996)]. This compound has proved to be an efficient substrate for semi-synthesis of 5-Isobutyl-3-methyl-4,5-dihydro-2(3H)-furanone which is an analogue of a commercially important naturally occurring flavoring agent whisky lactone (Scheme 17) [Sinha et al. (2007)].

Similarly, the oil obtained from the roots of Acorus calamus is rich source of several phenylpropenes like β-asarone (cis-2,4,5-trimethoxyphenylpropene). This olefin has proven...
to be inexpensive starting materials for synthesis of several value added products like propiophenones, cinnamaldehydes etc [Joshi et al. (2005); Joshi et al. (2006); Sinha et al. (2009)].

I.4.4 Microwave assisted organic synthesis

The traditional manner of heating reaction mixtures on a laboratory scale typically involved the use of isomantles, oil baths or hot plates by applying a reflux set-up. This form of heating is a rather slow and inefficient method for transferring energy into a reaction mixture, as it depends on convection currents and on the thermal conductivity of the various materials that must be penetrated. Moreover, it often results in the temperature of the reaction vessel being higher than that of the reaction mixture leading to wastage of energy. Consequently, the employment of more efficient sources of energy is one of the critical components of green chemical practices.

In this context, Microwave Assisted Organic Synthesis (MAOS) offers an attractive platform for enhancing the overall productivity of a synthetic pathway [Kappe (2004); Appukkuttan and Eycken (2006); Kappe (2008); Polshettiwar and Varma (2008)]. The microwave (MW) irradiation causes efficient internal heating by direct coupling of MW energy with molecules present in the reaction mixture [Loupy (2006); Kappe (2008)].

Some of the principal benefits of MAOS include:

➢ Drastic reduction in reaction times
➢ Improved yields and selectivity
➢ Higher energy efficiency
➢ Possibility of solventless reactions
➢ Operational simplicity

I.5 Objectives of present studies:

In view of the above discussion, it is evident that phenolics like phenylethanoids, phenylpropanoids along with 1,5-diphenylpenta-2,4-dien-1-ones and heteroaromatics constitute highly useful compounds with wide applications in pharmaceuticals, material science, flavor and fragrance domains etc.

The above compounds have been accessed through various synthetic methodologies. However, there is an urgent need to develop environment friendly synthetic methodologies.
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for such phenolics. In this context, the primary objective of this thesis was to develop new approaches for synthesis of some biologically important phenolic and heteroaromatic compounds. One of the major emphasis during above work involved the utilization of concepts and tools of green chemistry.

For the sake of convenience, the studies undertaken in this thesis have been divided into four chapters as mentioned below:

**Chapter 1**  
One-pot multicomponent C-C bond formation strategy for synthesis of hydroxylated stilbenoids

**Chapter 2**  
Ionic Liquid assisted metal free decarboxylation of heteroaryl and aryl carboxylic acid derivatives under microwave irradiation

**Chapter 3**  
One-pot two-step synthesis of aryl substituted dienones and enones from phenylpropenes under microwave irradiation

**Chapter 4**  
Microwave induced single step synthesis of α-aryl aldehydes from arylalkene derivatives in aqueous medium

I.6 References and Notes


