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Green methodologies in synthesis and natural product chemistry of phenolic compounds[†]

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A number of green methodologies employing microwave, ionic liquids, ultrasound, *etc* have been developed for the synthesis and isolation of diverse bioactive phenolics. The use of above green tools greatly improve the reaction performance and provides additional benefits like reduction in cost and waste besides replacement of hazardous chemicals.

Keywords: Green chemistry, phenolics, microwave, ionic liquids, antioxidant

Phenolic compounds constitute a wide range of biologically important compounds and further comprise of various sub-classes like phenylpropanoids, phenylethanoids, flavonoids, benzofurans, anthraquinones, coumarins, tannins, neolignans and may also bear functionalized alkyl side chains[1]. In fact, a number of abundantly available natural bioactive phenolics possess two to three carbon side chains and are termed as phenylethanoids and phenylpropanoids respectively. The various phenylethanoids and phenylpropanoids are important plant secondary metabolites derived from shikimic acid, a central molecule in the plant metabolism and occur in phenyl propanoid biosynthetic pathway[1]. The global interest in phenolic compounds has rapidly increased due to their possible role as natural antioxidants as well as the recognition of their wide ranging health promoting biological and pharmacological activities such as antibacterial, anti-inflammatory, antifungal, and anticancer activities[1]. In addition, phenolics are also being widely employed as flavouring and nutraceutical agents.

For instance, 4-hydroxy-3-methoxystyrene, a high valued FEMA GRASS (Flavor and Extract Manufacturer´s Association; Generally Regarded As Safe) approved flavoring agent, is isolated from a variety of plants such as *Hibiscus esculentus*, *Digitaria exilis, Citrus paradisi* and *Feijoa sellowiana*[2]. Similarly, substituted stilbenes are widely present in nature and have many biological activities[3]. For example, resveratrol, a phytoalexin (plant antibiotic) present in grapes and other fruits, is reported to play a role in the prevention of heart diseases and cancer[3]. Likewise, phenylpropanoids comprise of various phenolic derivatives like phenylpropenes, α-phenyl propionaldehydes, phenylpropanes, cinnamic acids, cinnamyl alcohols, cinnamaldehydes, cinnamic esters, *etc*. Phenylpropenes are isolated in high concentrations from the essential oil fractions of plant tissues and have a plethora of bioactive properties[4]. These find applications in various fields such as perfumary, flavours, cosmetics, pharmaceuticals and many others[5]. In addition, phenylpropenes have wide-spread synthetic applications for the formation of important bioactive molecules like α-phenyl propionaldehydes, propiophenones, cinnamaldehydes, phenylpropanols, lignan and neolignan, *etc*.

Owing to their immense importance, there has been a widespread interest in accessing the above phenolics, however, a full exploration has been severely hindered due to their minute concentrations in plant sources. Thus, there is an urgent need to develop new methodologies for synthesis and efficient isolation of bioactive phenolics.

On the other hand, there has been a growing realization in the academia and industry regarding the grave environmental ramifications of hazardous chemicals and processes. Consequently, the realm of synthetic organic chemistry has been witnessing a remarkable conceptual upheaval in the form of incorporating green chemical processes in synthetic

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design[6]. The edifice of green chemistry is built on the premise of a reduction in waste, materials, hazards, energy and cost involved the design of chemical processes[6]. Especially, the use of microwave and ultrasound assisted synthesis has come to the force in view of the unique benefits like energy efficiency, enhanced reaction rates and increased yields[6].

In this context, we have been making efforts to develop green methodologies for synthesis as well as efficient isolation of bioactive phenolics like phenylpropanoids and phenylethanoids and some of the highlights of above work would be presented in subsequent sections.

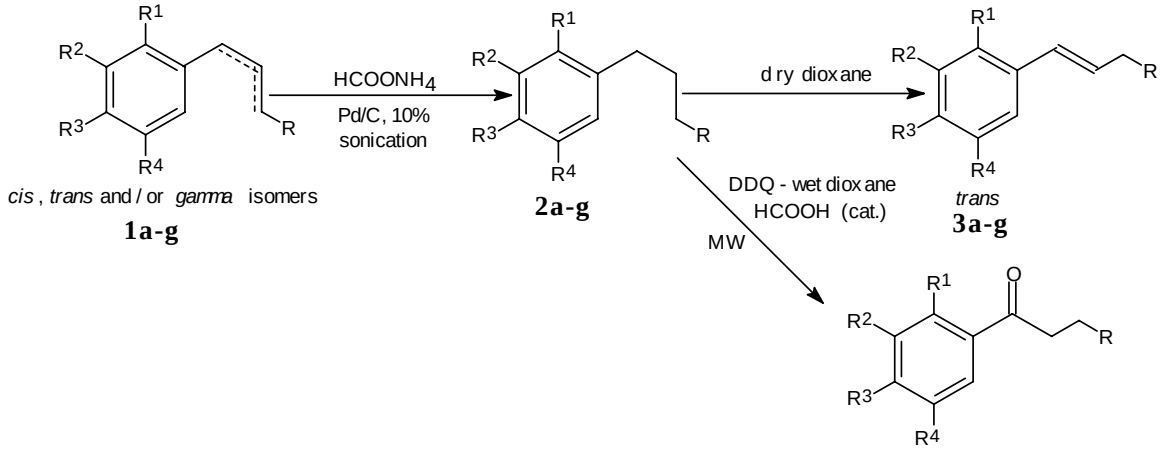
(A) Green approaches for bioactive phenylpropanoids and phenylethanoids

The phenylpropanoids[4] represent a diverse class of natural products and our interest has been focused on the development of bioactive phenylpropanoids like phenylpropenes, phenylpropanes, cinnamic acids, cinnamyl alcohols, cinnamaldehydes, cinnamic esters, *etc*. Similarly, phenylethanoids comprise of important bioactive compounds like styrenes, stilbenes, *etc*.

(i) Convenient synthesis of hypolipidemic active natural methoxylated (*E*)-arylalkenes and arylalkanones: The methoxylated phenylpropanoids and phenylbutanoids like (*E*)-arylalkenes (such as α-asarone) and arylalkanones (such as isoacoramone) are reported to be active hypolipidemic agents[7]. These natural compounds are also known to have a wide range of biological activities such as neuroleptic, anti-ulcerogenic, anti-atherogenic, anti-inflammatory activities. In this context, an ultrasound-assisted convenient method[7] was developed for the conversion of toxic methoxylated *cis*-isomer of arylalkenes into its hypolipidemic active *trans*-isomer (**Scheme I**).

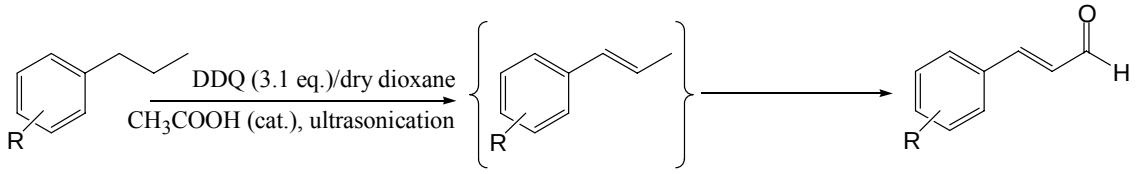
Treatment of *cis*-isomer or mixture of all three isomers with ammonium formate and 10% Pd/C gave arylalkanes which upon oxidation with DDQ in anhydrous dioxane containing a little amount of silica gel, provided (*E*)-arylalkenes in 42-72% yield depending upon the substituents attached at the aryl ring. The same method, upon addition of a few drops of water, provided hypolipidemic active arylalkanones (in 59-65% yield).

(ii) One-pot, two-step synthesis of (*E*)-cinnmaldehydes by dehydrogenation-oxidation of arylpropanes using DDQ: Cinnamaldehyde derivatives are common in nature and they possess remarkable biological properties such as antibacterial, antifungal, antitermitic, antioxidant and anticancer activities. Moreover, cinnamaldehydes are used to prevent



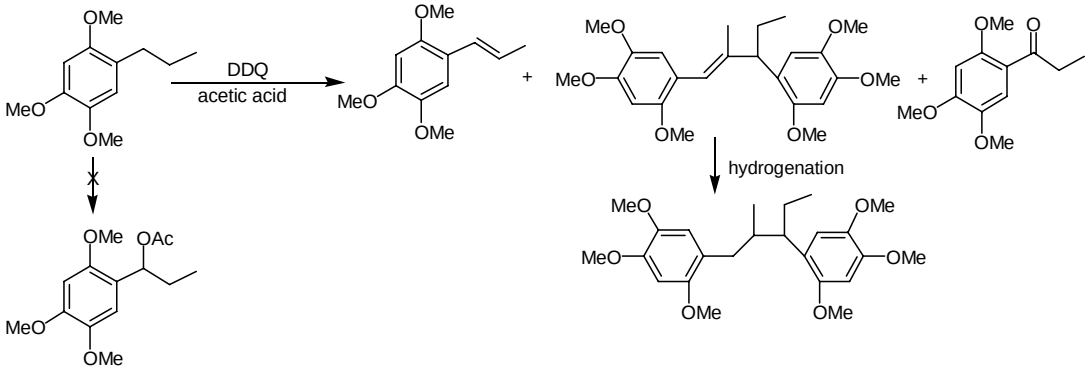
	R^1	R^2	R^3	R^4	R
(a)	OMe	H	OMe	OMe	H
(b)	H	OMe	OMe	OMe	H
(c)	H	OMe	OMe	H	H
(d)	H	(R^2+R^3)	-OCH_2O-	H	H
(e)	H	H	OMe	H	H
(f)	OMe	H	OMe	OMe	CH_3
(g)	H	OMe	OMe	H	CH_3
(h)	OMe	H	OMe	OMe	H
(i)	H	OMe	OMe	OMe	H
(j)	OMe	H	OMe	OMe	CH_3

Scheme I



Where
R= OMe, OEt, OCH_2O, OH etc.

Scheme II



Scheme III

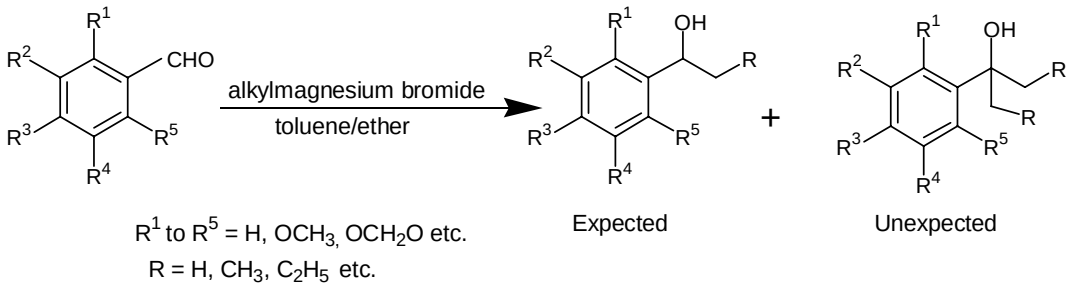
darkening of skin caused by UV rays of sun and also prevent hair-loss[8]. However, a majority of the prevalent protocols for synthesis of cinnamaldehydes suffer from poor yield, harsh reaction conditions and contamination with small amounts of the undesirable *Z*-isomer. Consequently, we have developed a general, efficient and new approach to the synthesis of cinnamaldehydes with *trans*-selectivity starting from arylpropanes (**Scheme II**, ref. 8). A one-pot two-step dehydrogenation and oxidation of arylpropanes with excess DDQ in dioxane containing a few drops of acetic acid gave (*E*)-cinnmaldehydes under ultrasonication.

(iii) Formation of neolignan by DDQ mediated dimerization of dihydroasarone: Neolignans and lignans are known for their wide-range of biological activities including hepatoprotective, harmone blocking, antibacterial, antifungal, plant growth regulator, anti-HIV, anticancer and antioxidant activities[9]. In the course of our efforts towards DDQ assisted oxidation of phenyl alkane derivatives, we have discovered a simple and economical process for preparing novel neolignans (3-ethyl-2-methyl-3-(2″,4″,5"-trimethoxy)phenyl-1-(2′,4′,5′-trimethoxy)phenyl-1-propene and (3-ethyl-2-methyl-3-(2",4",5"-trimethoxy)phenyl-1-(2′,4′,5′-trimethoxy)phenylpropane.

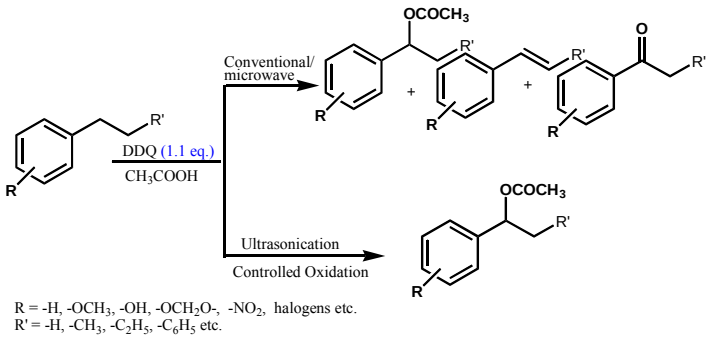
The methodology utilized hydrogenation of toxic β-asarone or calamus oil containing mixture of α,β and γ-asarone to obtain 2,4,5-trimethoxyphenyl-propane followed by reacting the above said compound with DDQ at a temperature in the range of 5-120°C for a period ranging from 30 min to 72 hr using acetic acid as solvent (**Scheme III**, ref. 9).

(iv) Unexpected formation of aryl dialkyl carbinol as a side product from the reaction of methoxyarylaldehydes with Grignard reagents

The Grignard reaction is a highly useful transformation in contemporary organic synthesis. However, the formation of various side products is one problem generally encountered. In most cases, the side products remain unrevealed and in others, where they are identified, numerous mechanisms underlying their formation create considerable ambiguity regarding their formation. From an industrial point of view, endeavors towards identification of such side products during the development of chemical processes for bioactive compounds holds considerable importance, as side product detection is highly crucial for quality approval by relevant agencies. During our attempts towards formation of secondary arylalkylcarbinols from the reaction of methoxyarylaldehydes with Grignard reagents, aryldialkyl carbinols were formed as unexpected side-products (**Scheme IV**, ref. 10).



Scheme IV

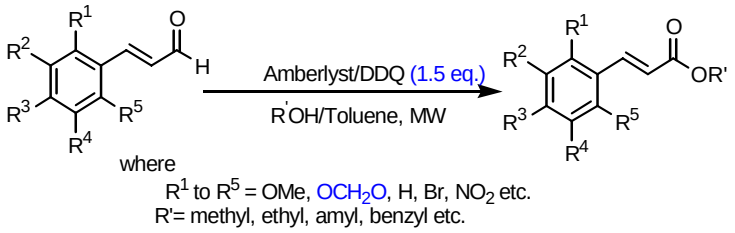


Scheme V

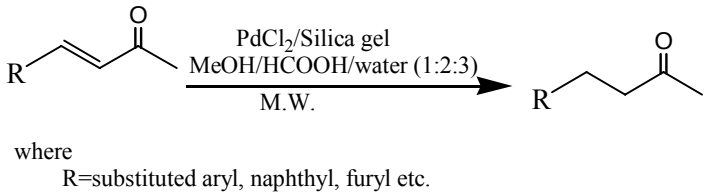
Consequently, we also investigated the mechanism of this unexpected formation of dialkyl carbinol and it is believed to proceed through an internal Canninzaro-type reaction of some of the secondary alcohol to afford the corresponding oxidized product.

(v) DDQ catalyzed benzylic acetoxylation of arylalkanes: The selective C-H bond activation of hydrocarbons constitutes one of the most versatile albeit challenging pursuits of organic synthesis. In particular, the controlled benzylic oxidation of arylalkane derivatives has remained a prominent area of interest due to the immense industrial importance and synthetic utility of the corresponding oxidation products like benzyl alcohols or acetates. Consequently, we have developed a DDQ catalyzed benzylic acetoxylation protocol wherein the application of ultrasound imparted exquisite control of the oxidation process as compared to conventional or microwave activation (**Scheme V**, ref. 11). The developed method provides a convenient and selective access to immensely important acetoxylated arylalkanes *in lieu* of the prevalent methods involving the formation of several competing oxidized products. In addition, the developed method could be a useful strategy for the synthesis of industrially important enantiopure benzylic secondary alcohols through chiral resolution of obtained acetoxylated products.

(vi) A chemoselective strategy for the preparation of (*E*)-cinnamic esters from cinnamaldehydes using heterogeneous catalyst and DDQ: (*E*)-Cinnamic esters are immensely important organic compounds due to their application in a wide range of industrial products such as plasticizers, graphics, lubricants, flavours, perfumes and cosmetics. These α,β-unsaturated esters possess various pharmacological activities including antioxidant, antimicrobial and anticancer activities, besides being useful in other synthetic applications[12]. Though, numerous methods have been reported for the preparation of α,β-unsaturated esters, however, most of the reported procedures require strong acids like sulphuric acid, hydrochloric acid and toxic chemicals such as dimethylsulphate, methyl iodide, diazomethane, which are environmentally hazardous and hence unacceptable. More importantly, none of the methods disclose a single step approach towards conversion of cinnamaldehydes into cinnamic esters, while simultaneously taking care of the compatibility of the process with other sensitive functional groups. In view of above, an efficient chemoselective protocol



Scheme VI

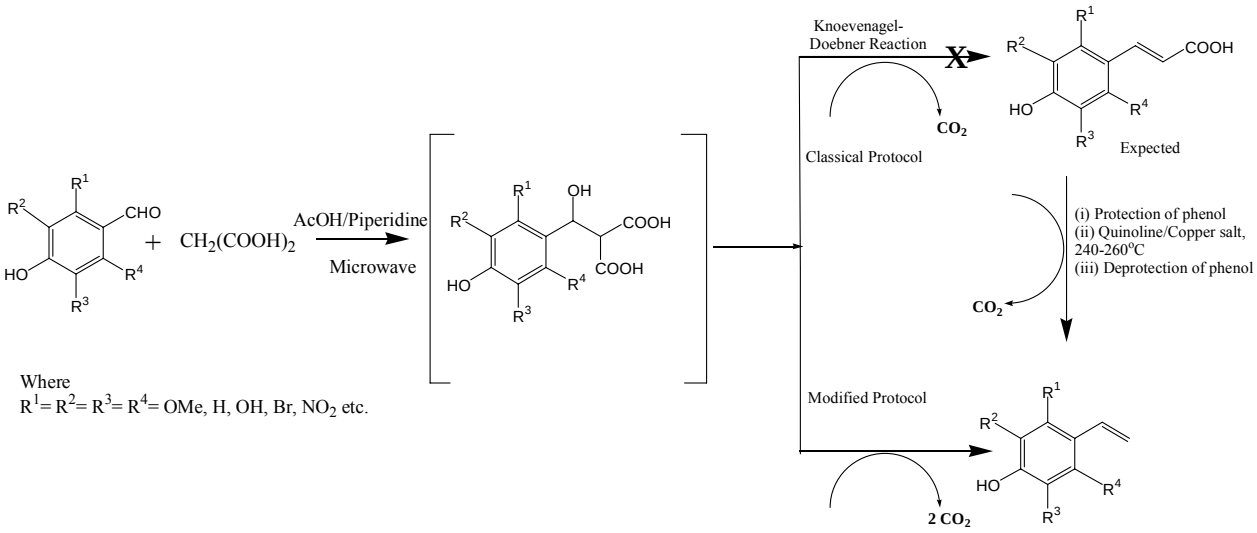


Scheme VII

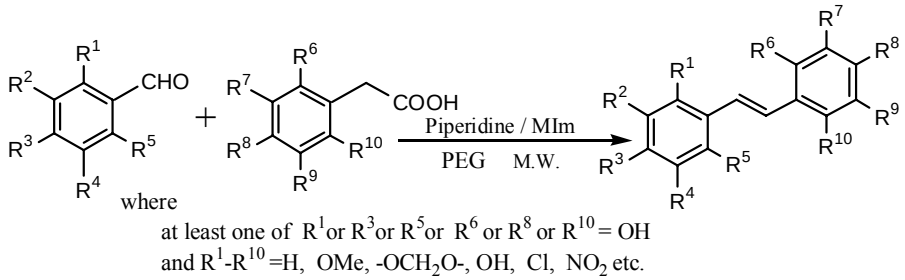
was developed for the synthesis of (*E*)-cinnamic esters from substituted cinnamaldehydes or cinnamyl alcohols using a combination of DDQ and heterogeneous catalyst under microwave irradiation (**Scheme VI**, ref. 12). The method showed remarkable selectivity for cinnamaldehydes over aliphatic and aromatic aldehydes. The results demonstrate that the developed protocol can be a useful synthetic tool for chemoselective esterification in total synthesis of complex organic compounds.

(vii) Chemoselective hydrogenation of olefinic bond of α,β-unsaturated carbonyl compounds in aqueous medium: The chemoselective reduction of α,β-unsaturated carbonyl compounds has remained an attractive area of organic synthesis due to a wide range of applications of the resulting saturated carbonyls as food sweeteners and in flavour, perfumery, and pharmaceutical industries. Among various available reduction protocols for the synthesis of these important dihydro compounds, catalytic transfer hydrogenation (CTH) has emerged most viable, mainly due to non involvement of highly flammable and explosive molecular hydrogen or metal hydride donors. However, reports on microwave-assisted chemoselective manipulation of double bond have utilized various organic hydrogen donors including commonly used inexpensive formate salt and resin supported formate. In this context, a microwave assisted mild and ecofriendly catalytic transfer hydrogenation process was developed to reduce various α,β-unsaturated carbonyl compounds into corresponding saturated carbonyl compounds in the presence of silica supported palladium chloride as catalyst and a combination of MeOH/HCOOH/H_2O (1:2:3) as hydrogen source within 22-55 min in moderate to excellent yield with 100% chemoselectivity (**Scheme VII**, ref. 13).

(viii) A new perspective on the classical Knoevenagel Doebner reaction: One-pot two-step synthesis of 4-vinylphenols from 4-hydroxy substituted benzaldehydes under microwave activation: 4-Vinylphenols, a class of functionalized styrenes, constitute one of the most extensively explored compounds due to their wide ranging applications in food and alcoholic beverages, flavouring substances and as intermediates in the preparation of various bioactive molecules, polymers and copolymers useful in coatings, electronic applications, ion exchange resins and photoresists, *etc*.[2] The development of a simple and efficient synthetic methodology for vinylphenols has been a difficult proposition due to the susceptibility of the hydroxy function towards polymerization. Consequently, a majority of the prevalent synthetic strategies comprise protection-deprotection steps for vinylphenols. In light of this, a new protocol was sought wherein the age-old Knoevenagel-Doebner method was modified to give commercially important vinylphenols in a single step from 4-hydroxy-benzaldehydes and malonic acid under microwaves



Scheme VIII

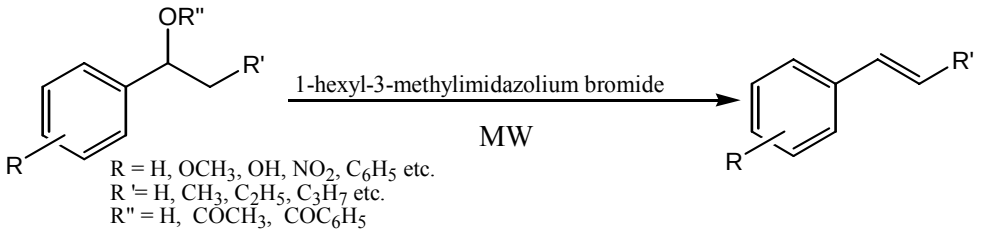


Scheme IX

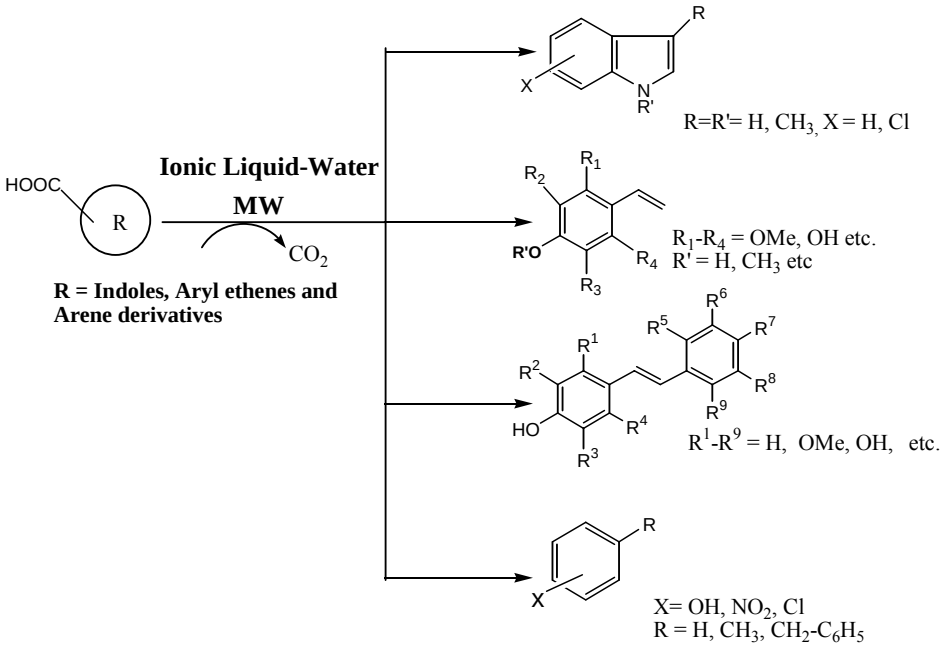
via an unprecedented simultaneous condensation-double decarboxylation (**Scheme VIII**, ref. 14). The developed method eliminates the need for toxic decarboxylating agents like quinoline and metal salts.

(ix) Mild and convenient one-pot two-step access to (*E*)-stilbenes from hydroxy-substituted benzaldehydes and phenylacetic acids under microwave activation: Hydroxylated stilbenes constitute an important class of natural compounds due to their wide-ranging biological activities, putative potential as nutraceuticals as well as their application in molecular photonics and optoelectronics[3]. Amongst the prevalent synthetic approaches towards these bioactive stilbenes, the Perkin reaction between benzaldehydes and phenylacetic acids in the presence of acetic anhydride and a base followed by decarboxylation with quinoline/Cu salt has remained a prominent method. However, a new facet to the classical Perkin reaction was discovered whereby an unusual simultaneous condensation-decarboxylation provides a mild and convenient one pot access to various bioactive stilbenes from hydroxy-substituted benzaldehydes and phenylacetic acids under microwave irradiation (**Scheme IX**, ref. 15). In addition, the method was extended towards the formation of some important methoxylated analogues of hydroxy stilbenes *via* an unprecedented one-pot condensation-decarboxylation-methylation process.

(x) Neutral ionic liquid as a green reagent and solvent for dehydration of benzylic alcohols: Dehydration of alcohols is a fundamental and extensively exploited transformation in organic synthesis due to the immense biological importance and synthetic utility of ensuing alkenes. The usual protocols for accomplishing the above dehydration employ various reagents like mineral acids, PTSA, oxalic acid, *etc*. However, a majority of the above protocols are limited by their incompatibility with substrates possessing acid sensitive functional groups and propensity for unwarranted side reactions. In order



Scheme X



Scheme XI

to develop a mild and efficient dehydration protocol for benzyl alcohols/acetate into the corresponding arylalkenes, an ionic liquid based protocol was developed. The method utilized a neutral and recyclable 1-hexyl-3-methylimidazolium bromide ionic liquid as a reagent and solvent to cleanly provide a wide range of olefins without the use of harsh and expensive Bronsted/Lewis acids (**Scheme X**, ref. 16).

(xi) A new protocol for metal free decarboxylation of *N*-heteroaryl and aryl carboxylic acids under aqueous conditions using ionic liquids: Decarboxylation constitutes an important and frequently desired transformation in living systems as well as in synthesis of diverse classes of bioactive organic and heterocyclic compounds as it confers a facile approach to modify the underlying carbon skeleton. In recent times, decarboxylation has also emerged as a new pivotal element to design carbon-carbon bond forming strategies. However, apart from the ambient enzymatic decarboxylative systems devised by nature, decarboxylation of various substrates in the context of organic synthesis has remained one of the most difficult transformations often requiring prior activation by metal catalysts besides the usage of harsh organic bases. We have found that ionic liquids provide a versatile platform for metal and quinoline free decarboxylation of various *N*-heteroaryl and aryl carboxylic acids under microwave irradiation in aqueous condition. The method was found to possess wide substrate scope towards synthesis of various pharmacologically and industrially important aromatic compounds including indoles, styrenes, stilbenes, nitro or hydroxy arene derivatives. The decarboxylation of indole and α-phenylcinnamic acids proceeded well without addition of any catalyst in neat [hmim]Br and [Hmim]PTSA respectively while addition of a mild base like aq. $NaHCO_3$ to [hmim]Br further improved the decarboxylation of hydroxylated cinnamic and aromatic acid substrates (**Scheme XI**, ref. 17).

Table I — Total phenolic content and radical scavenging activities of different extracts (for n=3)

	Maceration		Ultrasound		Microwave		Soxhlet	
	TP[a,b]	TEAC[a,c]	TP[a,b]	TEAC[a,c]	TP[a,b]	TEAC[a,c]	TP[a,b]	TEAC[a,c]
Seed	9.4±0.05	44.05±0.09[d]	15.6±0.39	93.74±0.80[d]	23.5±0.19	182.13±0.10[d]	21.9±0.11	166.16±0.48[d]
		128.03±0.63[e]		131.29±0.12[e]		282.75±0.12[e]		235.12±1.13[e]
Leaves	2.7±0.39	9.80±0.40[d]	5.9±0.39	13.72±0.41[d]	10.8±0.38	41.14±0.40[d]	9.7±0.35	37.16±0.46[d]
		17.52±0.12[e]		18.91±0.25[e]		56.82±0.19[e]		39.55±0.43[e]
Pulp	1.9±0.38	2.03±0.60[d]	3.8±0.19	4.86±0.60[d]	4.8±0.19	16.82±0.70[d]	4.4±0.18	6.24±0.64[d]
		6.97±0.16[e]		7.07±0.12[e]		10.11±0.63[e]		8.73±0.44[e]
Fruit	2.3±0.39	2.13±0.50[d]	4.4±0.39	6.13±0.30[d]	9.3±0.39	18.81±0.19[d]	4.9±0.35	8.33±0.28[d]
		14.28±0.31[e]		16.72±0.70[e]		28.40±0.19[e]		21.37±0.24[e]

[a]Data expressed as mean ± standard deviation (SD) of three replicates. [b]Data expressed as mg of GAE/g of plant material (DM basis). [c]Data expressed as mg of trolox equivalent/g of plant material (DM basis). [d] TEAC assayed by the ABTS method. [e]TEAC assayed by the DPPH method.

(B) Green approaches in natural product chemistry of phenolic compounds: In the course of our efforts towards chemo-profiling of various natural phenolics in medicinal plants the following results were obtained:

(i) *Vanilla planifolia*

Microwave- and ultrasound-assisted extraction of vanillin and its quantification by High-Performance Liquid Chromatography in *Vanilla planifolia*

Vanillin (4-hydroxy-3-methoxybenzaldehyde), a major component of natural vanilla, is an important flavouring agent used worldwide in many food products, perfumes and in pharmaceutical preparations. Some of the methods for extraction of vanillin include supercritical fluid extraction, solid phase micro-extraction (SPME), biphasic sonoelectrolysis, enzymatic extraction, liquid-liquid, liquid-solid extraction, *etc*. However, these techniques are very often time-consuming, involve use of large quantity of solvents and high capital investment. Consequently, a fast, environmentally benign and relatively cost-effective method employing MAE and UAE for the extraction of vanillin from pods of *V. planifolia* has been developed. Similarly, a simple HPLC method was also developed for the determination of vanillin in pods of *V. planifolia*, which requires minimal (0.001%) ortho-phosphoric acid in a binary solvent system of ACN and water, and a common stationary phase (RP-18) which gives good separation and peak shapes. The method is suitable for the quantification of vanillin in vanilla extracts and other food and perfumery items[18].

(ii) *Hippophae rhamnoides* (Seabuckthorn)

Microwave-assisted efficient extraction of different parts of *Hippophae rhamnoides* for the comparative evaluation of antioxidant activity and quantification of its phenolic constituents by Reverse-Phase High-Performance Liquid Chromatography (RP-HPLC): *Hippophae rhamnoides* has been recognized as a versatile nutraceutical crop with diverse uses, and all parts of this wonder plant are considered to be good source of a large number of bioactive compounds including carotenoids, tocopherols, sterols, flavonoids, lipids, vitamins, tannins, minerals, *etc*. In the course of our efforts towards chemical investigation of *Hippophae rhamnoides*, the outcome of different extraction procedures (microwave, ultrasound, soxhlet, and maceration) on the antioxidant activity of seeds, leaves, pulp, and fruits of *Hippophae rhamnoides* (sea buckthorn or SBT) was investigated by two different bioassays: 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) diammonium salt (ABTS) and 2,2′-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging assays. The SBT extracts were found to possess strong antioxidant activity measured in terms of TEAC (2.03-182.13 and 6.97-282.75 mg/g) with ABTS and DPPH assays, respectively. In general, the antioxidant capacity of microwave-assisted extracts was found to be significantly higher than those obtained by ultrasound-assisted extraction (UAE) and maceration while being slightly higher than soxhlet extracts (**Table I**). The results demonstrated the practical feasibility of MAE to substitute the traditional time-consuming techniques for efficient extraction of antioxidative compounds to provide nutraceutical-rich formulations[19].

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