FINAL WORK DONE REPORT ON MAJOR RESEARCH PROJECT

(From 1 April 2013 to 31 March 2017)

'NEW METHODOLOGIES FOR SYNTHESIS AND ANTI-MICTROBIAL EVALUATION OF HETEROCYCLIC COMPOUNDS VIA MULTI-COMPONENT REACTIONS'

Acknowledgement:

First and foremost I want to thank UGC, New Delhi for sanctioning me this project. Due to this financial support we are able to do good quality of research work proposed in initial proposal and we have successfully completed this project with four international publications.

I take this opportunity to thank Prn. Abhaykumar Salunkhe, Chairman and Smt. Shubhangi Gawade, Secretory, Shri Swami Vivekanand Shikshan Sanstha Kolhapur for providing necessary facilities and encouragement.

Objectives of Project:

As MCRs have considerable advantages in organic synthesis, hence we can use this technique as Greener Technology for synthesis of new organic compounds. We can also develop new routes for the synthesis of biologically active heterocycles by using different techniques such as use of microwave irradiation methods, ultrasonic technique, cost effective natural as well as organocatalysts, ionic liquids, some supported reagents, solvent free reactions, etc through multicomponent reactions as green approach.

Under this project work some new compounds will be synthesized by applying different methods. Synthesized compounds are to be characterized by IR, NMR, crystallography and mass spectroscopy and tested for their antifungal and antibacterial activity.

Methodology:

1. Use of eco-friendly natural as well as organocatalyst in MCRs for the synthesis of targeted heterocyclic compounds.
2. Water promoted organic synthesis for heterocyclization.
3. Solvent-free approach for synthesis of heterocyclic compounds.

4. Use of microwave technique for targeted heterocyclic compounds.

5. Use of ultrasound technique for heterocyclization.

6. Use of inorganic solid-supported reagents in organic synthesis.

7. Applications of ionic liquids in MCRs for the synthesis of targeted heterocyclic compounds.

8. Application of rare earth triflates in Heterocyclic Synthesis.

Work done at the completion of the Major Research Project

Development of non-hazardous synthetic methodologies for organic transformations is nowadays one of the latest challenges in the light of growing awareness for the cleaner environment. The greener, more sustainable, at the same time more efficient, eco-friendly and economical methods should be designed to minimize the use of toxic chemicals, hazardous waste, to meet with the needs of safe environment. By shifting to new methodologies, one can achieve pure products with good yield avoiding use of hazardous materials and toxic solvents.

While designing new methodologies, different criteria should be taken into consideration such as suitable reaction media, conversion of all materials into products, minimization of energy requirement and use of renewable raw materials to avoid formation of toxic byproducts.

Various methods used for organic transformations are supported by a prevailing modern synthetic technique, known as multicomponent reactions (MCRs) or one-pot synthetic technique, in which more than one component are converted into the product. In contrast to the multistep synthetic technique, the MCRs require reduced working time and energy with maximum yield of final products. MCRs are useful in the synthesis of various complex products starting from simple reactants, avoiding multiple steps. A number of organic compounds comprising various useful properties such as imidazoles[1], pyridines[2], quinazolines[3], chromenes[4], triazoles[5], benzodiazoles[6] and so on can be synthesized by cost-effective multicomponent reactions starting with simple precursors. Many important name reactions are developed viz. Hantzsch dihydropyridine synthesis,[7] Biginelli reaction,[8] Mannich reaction[9], Ugi reaction,[10] Passerini reaction[11] which use MCR technique for easier synthesis of complex products.

Designing of new clean and green methods for chemical transformations, should be done in order to fulfill the need for cleaner environment, by following different ways to minimize the energy consumption and to convert all of the starting materials into products, using suitable reaction media and raw materials from renewable resources to avoid the formation of toxic byproducts.

While taking into account all the above views in the light of Green Chemistry, the use of natural feedstock play an important role in the development of environmentally benign chemical processes. Different natural materials are used as solid support as well as catalysts in a large number of reactions promoting the formation of final products. Natural materials such as clays, zeolites, enzymes, and different plant materials such as leaves, fruits, roots are used effectively in numerous chemical transformations.

In recent times, an important class of natural materials involving clays and zeolites has received significant awareness of the researchers working in the field of synthetic chemistry.[12] Some types of clay can be employed as acid or base catalysts while carrying out series of organic synthetic reactions.

Jayachandran et. al.[13] have demonstrated an efficient process for highly regioselective chlorination of arenes using Cl_2 or SO_2Cl_2 as chlorinating agent to afford *p*-chlorinated products predominantly with exceptional *o*-chlorinated product in presence of natural Kaolinite Clay. Gadekar et al.[14] have synthesized polyhydroquinoline derivatives by refluxing the reaction mixture in presence of ethanol using Scolecite, a natural calcium zeolite, as catalyst. Habibi et al.[15] have developed an efficient procedure using Natrolite zeolite $Na_2[Al_2Si_3O_{10}]\cdot2H_2O$, as a reusable heterogeneous catalyst for the preparation of 1-substituted tetrazoles. Khezri et al.[16] have developed a new method for efficient carbon–carbon double bond formation via Knoevenagel condensation using red mud packed in a column. Red mud (RM) is generated as a by-product during the production of alumina from bauxite ore. Cobzaru[17] et al. have prepared the catalytic material from natural clinoptilolite by ion exchange and acid treatment. This catalyst was used in the gas phase conversion of acetaldehyde and formaldehyde into acrolein. Sebti and others[18] have described natural phosphate (NP) catalyzed Claisen–Schmidt condensation between acetophenone and arylaldehyde at room temperature with or without a solvent to afford the desired product. The condensation is carried out in the presence of NP alone, activated by water, benzyltriethylammonium chloride and both.

Currently biocatalysis is an emerging area in organic transformations and fulfills many criteria of green chemistry due to significant characteristics of biocatalysts; they are non-toxic, they operate with high selectivity, decrease the waste production, lower energy consumption, use aqueous reaction media, and they are available from renewable feedstocks[19]. Due to these advantages, use of enzymes and micro-organisms in organic reaction is increasing day by day.

Borse et al.[20] have developed a simple and efficient method for Knoevenagel reaction to synthesize trisubstituted electrophilic alkenes, using lipase as a biocatalyst. For this study, they have used lipases from *Aspergillus oryzae* and *Rhizopus oryzae* as biocatalysts. Xie et al.[21] have used acidic protease from *Aspergillus usamii* (AUAP) to catalyze the direct aldol reactions between aromatic aldehydes and cyclic ketones in acetonitrile (MeCN) in the presence of water to yield aldol condensation product. By following this method, the enantioselectivities of up to 88% ee and diastereoselectivities of up to 97:3 (anti/syn) are achieved.

Tang et al.[22] have introduced trans glutaminase as catalyst for Henry reactions of various aldehydes with nitroalkanes to give nitroalcohols which results into good yield even at room temperature.

Ferraz et al.[23] have reported bioreduction of substituted α-tetralones to afford tetralols, using *Daucus carota* root. They used freshly cut root sterilized by washing in 2% NaOCl. Tetralones dissolved in mixture of acetonitrile and ethanol, which was then added to suspension of *Daucus carota* roots in phosphate buffer. The mixture was incubated at 35ºC for 4 days. Laxmi et al.[24] have explained asymmetric reduction of heteroaryl methyl ketones to corresponding alcohols using *Daucus carota* root. Li et al.[25] have carried out chemoselective reduction of aromatic nitro compounds to the corresponding hydroxylamines and amines catalyzed by plant cells from a grape (Vitis vinifera L.). They have also compared the reduction using plant cells of maize, tomato, banana, and many others. Bertini et al.[26] have reduced a series of aliphatic and aromatic aldehydes and ketones using *Glycine max* seeds (soyabean). The biotransformation of aromatic aldehydes in water, at room temperature afforded the corresponding alcohols [13a, 13b] in excellent yields. Salunkhe et al.[27] have developed a simple, cost-effective method for the acylation of amines using aqueous extract of pods of *Acacia concinna* fruits to afford N-acylated products. Fonseca et al.[28] have reduced aliphatic and aromatic aldehydes and ketones using coconut

(*Cocos nucifera*) juice. The reduced products were obtained in excellent yields and with very high enantiomeric excess.

Nature is flourished with a variety of plants which are furnished with a number of certain chemical constituents that are biologically as well as medicinally important. The parts of plants such as fruits, leaves, roots have attracted more attention due to their immense use as effective medicines. Their medicinal significance is due to some important chemical constituents present in them. Besides this, the researchers are trying to make use of these substantial characteristics of natural plants while designing new methods for organic transformations, which can make the processes eco-friendly and fulfill the conditions for greener chemistry. The organic synthetic transformations using these natural materials are found to be competent and characterized by simple workup, non-toxicity, less waste production and pure products as compared to the conventional methods.

Utilization of constituents obtainable from natural resources have exploited the route for the development of new methodologies which are eco-friendly and economical also. These processes are characterized with simple workup, cleaner procedures, non-toxic waste materials which fulfill the requirements for greener methods.

By keeping in this in view, we have decided the utilization of natural sources for organic transformation. Initially we focused our attention on selection of plant material based on their pH. We observed that, adequate quantity of citric acid gives low pH to fresh Lemon extract, hence it can be used as an efficient acid catalyst in organic transformations. It is also found to be effective in presence of mild and less polar organic solvents at optimum temperature as well as at higher temperatures. Likewise, Lemon extract is completely soluble in water, and found to be suitable as Bronsted acid type catalyst. On the other hand, its water solubility adds to ease during separation of catalyst from the reaction mixture.

Due to the above mentioned important properties, Lemon extract can be used as an efficient acid catalyst for different organic transformations. This natural catalyst is easy to operate, non-toxic, cost efficient, easily available from natural resources and can be effectively used as greener catalyst while developing new methods for organic transformations.

For utilization of this natural material, initially, we have done detailed literature survey of some pharmaceutically important chemical moieties, synthesized by acid

catalyzed MCR strategy, such as benzopyrans (I), octahydroxanthenes (II), benzimidazole (III) and imadiazoles (IV) etc.
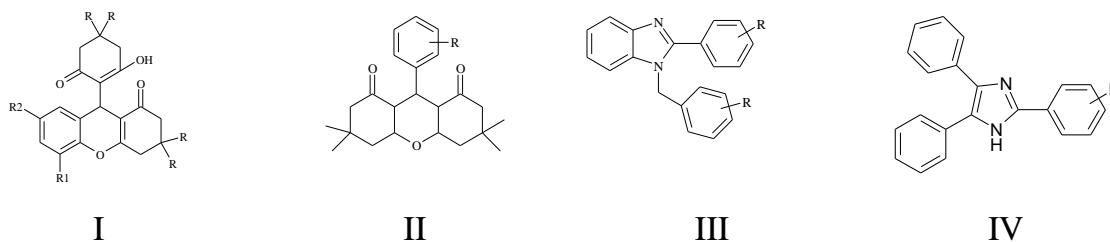

| I | II | III | IV |

Fig. Acid catalyzed pharmaceutically important chemical moieties

Recently, benzopyran derivatives have attained considerable significance in potential biological and pharmacological target compounds.[33] The prime driving force in this area is the need for their anti-estrogenic activity[34], insulin-sensitizing activities[35], selective thrombin inhibitory activity[36], antimicrobial activity,[37] antibacterial activity,[38] and hypoglycemic activity. The construction of new analogs of heterocyclic compounds is a major challenge in synthetic organic and medicinal chemistry. Because of their broad spectrum of biological interest, chemists have developed a few methods for the synthesis of benzopyran derivatives.[39]

In this work, we have developed a new, economical and straightforward bioorganic approach (Scheme 2) for benzopyrane synthesis via Knoevenagel condensation and tandem Knoevenagel-Michael reaction which represents a highly efficient and environmental benign system. Apart from this simplicity of product separation and utilization of biodegradable catalyst obtained from renewable resource are the significant advantages of this protocol. This new acidic dispersant should thereby provide attractive alternative to the harmful corrosive acids. However in true sense, we think that biosurfactant doesn't offer only a synergistic effect of acidic nature and surface activity but might be combination of many other factors. Hence to have a good contribution in innovation of green chemistry, we will lengthen our research to have more exposure to natural dispersant mediated organic transformations. All details of work done are presented in paper published in ***RSC Advances,*** 2015, 5, 84610-84620 and which is enclosed at the end.
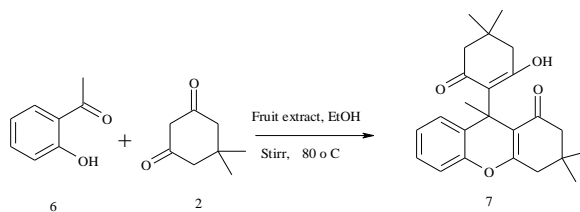
Scheme 2: Standard model reaction 2-hydroxy benzaldehyde and dimedone reactants.

The xanthenes are the heterocycles having oxygen as heteroatom are an important family of organic compounds because they have wide range of biological and pharmaceutical properties such as anti-inflammatory,[29] anti-depressants and antimalarial agents.[30] Furthermore, these compounds have been used as dyes,[31] and pH- fluorescent materials for the visualization of biomolecular assemblies.[32] There are several reports available in the literature for the preparation of various xanthene derivatives. One of the commonly used method for the synthesis of xanthene derivatives however involves the condensation of aldehydes with 1,3-cyclohexanedione or 5,5-dimethyl-1,3-cyclohexanedione.

According to our research project objectives, we have achieved an efficient, rapid, one-pot synthesis of 1,8-dioxo-octahydroxanthenes and intermediate arylmethylene bis(3-hydroxy-2-cyclohexene-1-one) derivatives *via* a multi-component reaction of aldehydes, 1,3-diketone, malononitrile using Lemon extract as a natural acid catalyst (Scheme 1).

In this work, we describe an efficient and clean method for the preparation of arylmethylene *bis*(3-hydroxy-2-cyclohexene-1-ones) via domino Knoevenagel-Michael reactions at room temperature and 3,3,6,6-tetramethyl-9-aryl-3,4,5,6,7,9-hexahydro-2*H*-xanthene-1,8-diones by Knoevenagel-Michael-cyclodehydration reactions at refluxing condition in ethanol. These procedures offer several advantages such as use of inexpensive green catalyst, operational simplicity, minimal environmental impact, and high yield. Thus both of these syntheses are greener in their approach as does not produces by-products along with the use of ethanol as a solvent which makes this among the attractive and practical protocols for the syntheses of either of the products. All details are presented in paper communicated to Journal of Chemical Science which is enclosed at the end.
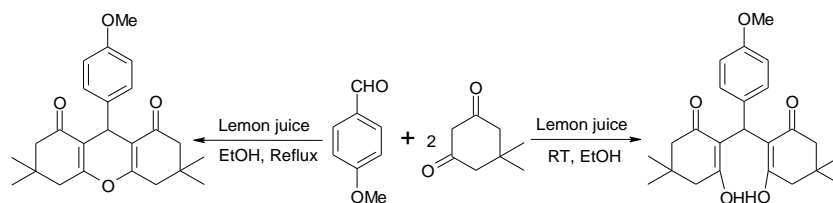
Scheme 1: Synthesis of 1,8-dioxo-octahydroxanthenes and their open chain analogues.

Benzimidazole moiety exhibits significant activity against several viruses such as HIV,[40] herpes (HSV-1),[41] RNA.[42] Benzimidazoles are also being developed as DNA minor groove binding agents with antitumor activity,[43] anticancer activity.[44] Their diverse applications comprise their role as potential angiotensin II inhibitors,[45] 5-lipoxygenase inhibitors for use as novel anti-allergic agents,[46] factor Xa (FXa) inhibitors,[47] and ADP-ribose polymerase (PARP) inhibitors.[48] Several publications reports benzimidazole-containing compounds showing biological activities such as selective neuropeptide YY1 receptor antagonism.[49] In addition, several substituted benzimidazole derivatives have been recently reported to have commercial applications in veterinarian medicine as antihistaminic.[50] The biological and synthetic significance places this scaffold at a prestigious position in the medicinal chemistry research.

By keeping this in view, we have reported bio-based, Brønsted acid type, bio-surfactant catalyzed green, convenient and selective method for the synthesis of 2-aryl-1-arylmethyl-1*H*-benzimidazoles using o-phenylenediamine and aromatic aldehydes (Scheme 3). The structures of final compounds were elucidated by IR, ^{1}H NMR, ^{13}C NMR spectroscopy. The green features of this method includes the use of biodegradable catalyst obtained from renewable resource ie *Citrus Limonium* extract as bio-surfactant type Brønsted acid, which provides a micellar media for effective cyclocondensation, good to excellent yield, high selectivity, tolerance of several common functional groups, avoidance of toxic solvent in the reaction as well as isolation stage. The critical micellar composition (cmc) of bio-surfactant was determined by conductivity method and visualized by light microscopy measurment. Employment of ethanol as co-surfactant emphasizes the convenience and economic viability of the method. All details of work done are presented in paper accepted by **Letters in Organic Chemistry** and which is enclosed at the end.
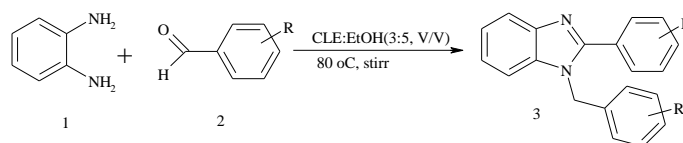
Scheme 3. Synthesis of benzimidazoles

Pharmacology:

In-vitro evolution of antibacterial activity was carried out for synthesized benzimidazole and imidazole derivatives and results are summarized in Table 1. The antibacterial activity was studied by selecting Gram-positive (*Staphylococcus aureus*) and Gram-negative (*Escherichia coli*) bacteria via agar well diffusion method. The zone of inhibition if any was then measured in mm for the particular compound and specific organism.

The bacterial inoculums was uniformly spread using sterile cotton swab on a sterile Petri dish MH agar. Three serial dilutions were prepared in different concentrations of 500, 300 and 100 mg/mL for synthesized derivatives and two serial dilutions were prepared concentrations of 100, 50 mg/mL for pure substance. 50 µL of compounds were added to each of the 3 wells (5 mm diameter holes cut in the agar gel, 25 mm apart from one another). The systems were incubated for 24 h at 36ºC ± 1ºC, under aerobic conditions. After incubation, confluent bacterial growth was observed. Inhibition of the bacterial growth was measured in mm.

The bacterial strains used were of non-invasive species of their genera and thus applicable for analytical work.

Staphylococcus aureus and *Escherichia coli* are among the most prevalent species of gram-positive and gram-negative bacteria, respectively, that induce clinical mastitis. *S. aureus* and *E.coli* are the main causes of bloodstream infections (BSIs) in humans. The microbial resistance of *E. coli* causing BSI is increasing alarminr across the world, while meticilin-resistant *S. aureus* decreasing in several countries. They are also common bacteria which causing food poisoning and therefore, for this study we have selected these two bacteria for the study.

Table 1. Zone of inhibition against *S. aureus* and *E. coli* in mm.

Product	Staphylococcus aureus			Escherichia coli		
	Conc. in ppm			Conc. in ppm		
	100	300	500	100	300	500
3a	--	--	5mm	--	--	3mm
3b	4mm	7mm	15mm	3mm	6mm	13mm
3c	--	--	3mm	--	--	2mm
3d	--	--	2mm	--	--	2mm
3e	--	--	2mm	--	--	3mm
3f	5mm	8mm	13mm	5mm	9mm	14mm
3g	7mm	12mm	18mm	9mm	13mm	19mm
3h	--	4mm	7mm	--	4mm	5mm
3i	--	--	5mm	--	--	5mm
3j	--	3mm	8mm	2mm	6mm	10mm
3k	3mm	6mm	10mm	3mm	7mm	9mm
3l	--	3mm	7mm	--	2mm	6mm
3m	11mm	16mm	20mm	11mm	15mm	19mm
3n	--	3mm	4mm	--	3mm	4mm
3o	8mm	11mm	16mm	7mm	10mm	15mm
3p	--	4mm	5mm	--	3mm	7mm
3q	2mm	5mm	8mm	6mm	10mm	15mm
3r	--	3mm	5mm	--	3mm	6mm
6a	--	--	5mm	--	--	3mm
6b	4mm	7mm	15mm	3mm	6mm	13mm
6c	--	--	3mm	--	--	2mm
6d	--	--	2mm	--	--	2mm
6e	--	--	2mm	--	--	3mm
6f	5mm	8mm	13mm	5mm	9mm	14mm
6g	7mm	12mm	18mm	9mm	13mm	19mm
6h	--	4mm	7mm	--	4mm	5mm
6i	--	--	5mm	--	--	5mm

6j	--	3mm	8mm	2mm	6mm	10mm
6k	3mm	6mm	10mm	3mm	7mm	9mm
6l	--	3mm	7mm	--	2mm	6mm
6m	11mm	16mm	20mm	11mm	15mm	19mm
6n	--	3mm	4mm	--	3mm	4mm
6o	4 mm	8mm	13mm	4 mm	10mm	12mm
Diameter of Zone of inhibition in mm					

The applicability of the this protocol is further extended to synthesis of highly substituted imidazoles by performing one-pot condensation in LE:EtOH (1:1, v/v) at 80 ºC (Scheme 4). The feasibility of the reaction is tested on various aromatic aldehydes with Benzil and ammonium acetate in good yield. In all cases, the products are isolated and are characterized by their IR, ^{1}H NMR, ^{13}C NMR spectral data. All details of work done are presented in paper accepted by **Letters in Organic Chemistry** and which is enclosed at the end.
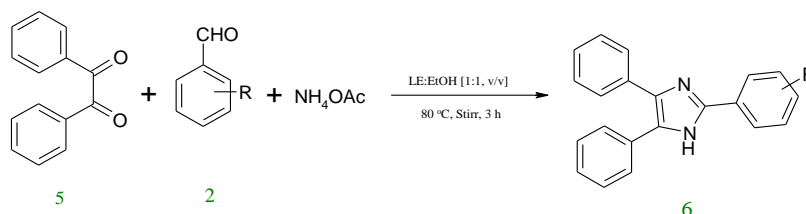

Scheme 4. Synthesis of 2, 4, 5-trisubstituted imidazole derivatives.

With success achieved in synthesis of benzopyrans, octahydroxanthenes, benzimidazole and imidazoles by employing Lemon extract as natural catalyst, we then focused our attention towards investigation of another natural sourced catalyst and we successively utilized Bael fruit ash water extract for heterocyclization.

4*H*-Benzochromene and 4*H*-chromene derivatives have received significant attention in organic chemistry due to their biological and pharmaceutical properties such as antimicrobial,[51] antiviral,[52] sex pheromone,[53] antitumor,[54] anti-inflammatory,[55] anti-tubercular,[56] and cancer therapy.[57] Indeed, vegetables and edible fruits are the food resources that are being characterized by natural products, containing chromene moiety in their structure.[58]

A facile, one-pot three-component protocol for the synthesis of 2-amino-4*H*-chromene derivatives has been demonstrated using Bael Fruit Extract (BFE) as a natural sourced catalyst in green reaction medium. This method offers a mild, efficient and highly economical protocol since the reaction proceeds in natural BFE-catalyst at room temperature under aerobic conditions at very short reaction time (30 min) under ligand/external catalyst/external promoter-free conditions and, therefore, it is an evergreen and environmentally sound alternative to the existing protocols. The catalyst was obtained by thermal treatment followed by water extraction to rind of *Aeglemarmelos* (Bael) fruit. It was also found to be clean, high-yielding and having ability to carry out large scale synthesis.

During this study, bael fruits were obtained from the local area and species were authenticated by the Department of Botany and the catalyst was obtained by thermal treatment. For this, initially rind of dry fruits was broken into small pieces manually with a knife, and then thermally treated at heating rate 2 ºC min $^{-1}$ in muffle furnace to 900 ºC and this temperature was maintained for 3 h. The thermal treatment had two parts: in the first part, most of the organic materials were burnt out for 30 minutes, whereas in the second part it was transformed into soft ash. Further, the BFE was suspended in distilled water and then carefully stirred for 1 h at room temperature. The mixture was then filtered to get clear extract and denominated as BFE, which was found to be alkaline (pH = 12.6). The efficiency of the catalytic medium was evaluated by the reacting naphthols, aromatic aldehyde and malononitrile in truly nontoxic conditions using the natural feedstock BFE at room temperature and in the absence of any other ligands or promoters. (Scheme 5).
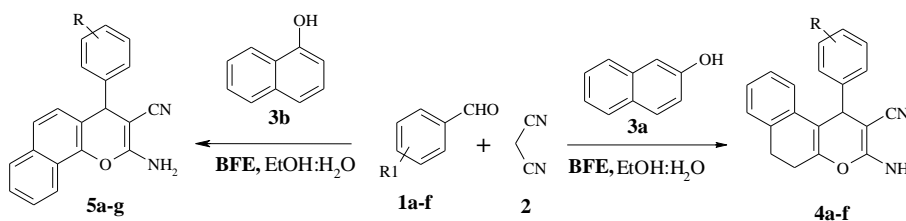
**Scheme 5: Synthesis of 2-amino-4*H*-benzochromenes using BFE catalyst.**

Inspired by these tempting results obtained for cyclocondensation of 4H-benzochromenes, we extended the same protocol for synthesis of 2-amino-4H-chromenes reacting various salicylaldehydes with malononitrile (or ethylcyanoacetate) and nitromethane (Scheme 6). However, the three-component reaction of salicylaldehyde, malononitrile (or ethylcyanoacetate) and nitromethane required longer reaction times

compared to the reaction of salicylaldehyde with malononitrile (or ethylcyanoacetate) under similar reaction conditions. All details of work done are presented in paper published in *RSC Advances,* 2017, 7, 7315 and which is enclosed at the end.
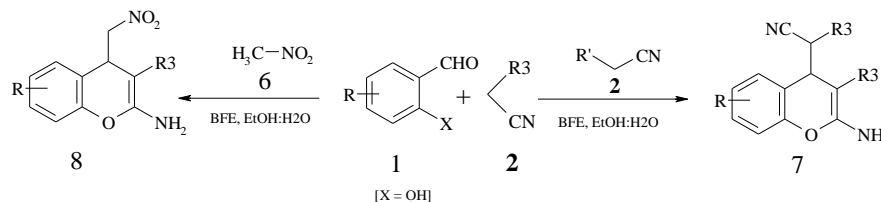

Scheme 6: Synthesis of 2-amino-4*H*-chromenes using BFE catalyst.

Furthermore we also continued our efforts for utilization of BFE, this amazing green medium for other cyclocondensation. To our most expectation we got excellent result for the synthesis of tetrahydro-chromeno [4,3-b] chromene-6,8-dione derivatives (Scheme 7). The work in under process and we hope this work will be accepted in reputed journal in future.
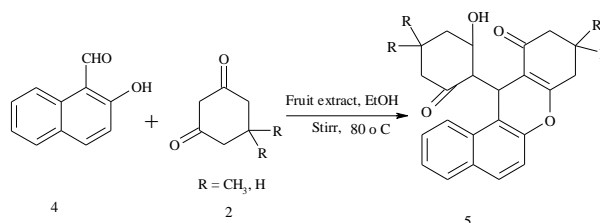
**Scheme 7: Standard reaction of 2-hydroxy naphthaldehyde and dimedone reactants.**

On the other hand, we also achieved utilization of citric acid as organocatalysts in mult-component reactions for heterocyclization. In this report, a simple and efficient protocol have been developed for the synthesis of 12-aryl-8,9,10,12-tetrahydrobenzo[a] xanthen-11-one derivatives employing a one-pot three-component reaction of aldehydes, 2-naphthol and dimedone in the presence of citric acid under solvent-free condition at 120ºC. The protocol was also extended for the synthesis of 14-aryl-*14H*-dibenzo [*a,j*] xanthenes by employing 1:2 proportion of aldehyde and 2- naphthol, to afford excellent yield in short reaction time (Scheme 8). All details of work done are presented in paper published in *Indian J Chemistry, Sec. B,* 2014, 53B, 1185-1193 and which is enclosed at the end.
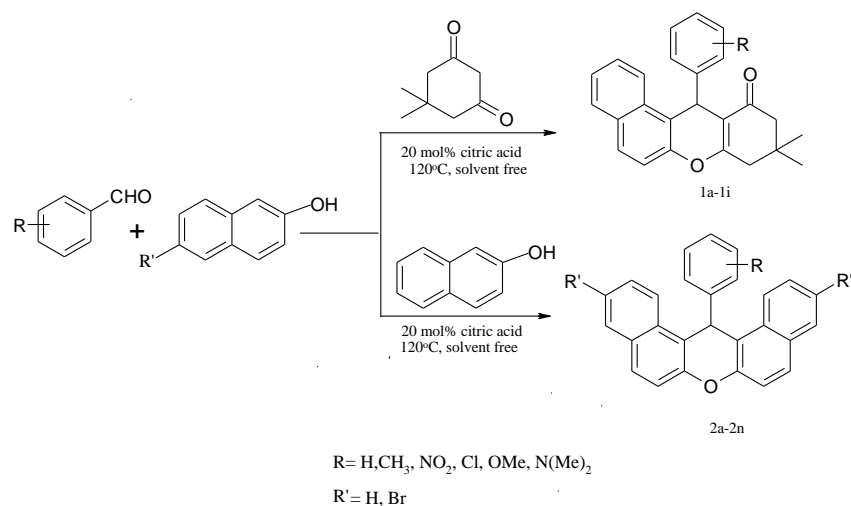
Scheme 8: Synthesis of xanthene from aldehyde, dimedone and 2-naphthol

Calcined egg shell (CES) is another natural, heterogeneous base catalyst, we are reporting here for one-pot four component synthesis of pyrano[2,3-c]pyrazoles and their derivatives in water at room temperature (Scheme 9). This nonconventional catalyst was obtained from renewable resources by simple calcinations of waste egg shell and characterized by FT-IR, XRD, DTA/TGA, and SEM techniques. A very simple protocol was followed in the reaction process. This strategy was also providing high yield and good recyclability of the catalyst.

Functionalized pyrano[2,3-c]pyrazoles are an important class of N-heterocycles because the core fragment is constituted by a great variety of natural products and biologically active compounds. The latter compounds, which have many pharmacological properties including anticancer[59], antimicrobial[60], anti-inflammatory[61], insecticidal and molluscicidal activities[62]. Furthermore, they shows potential inhibitors of human Chk1 kinase[63]. Therefore, the synthesis of pyrano[2,3-c]pyrazole and their derivatives has attracted much attention in organic synthesis.
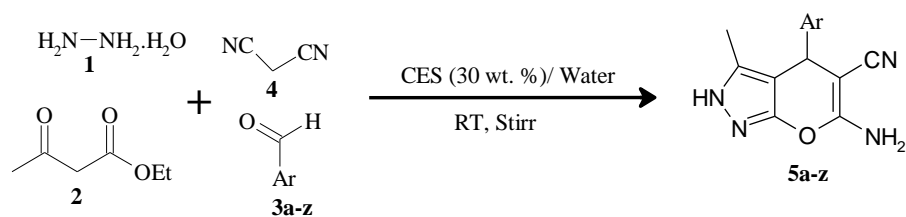

Scheme 9: Synthesis of pyrano[2,3-c]pyrazoles.

3. Pyridine ring systems represent an important class of compounds[64] not only for their theoretical interest but also many of these compounds display strong biological activity and constitute the skeleton of some alkaloids[65], of some antitumor antibiotic[66]. Hence, their synthesis has received much attention.

Recently, several procedures for the preparation of 2-aminochromenes have been described. Various catalysts such as piperidine[67], morpholine[68], CTACI (cetyl trimethyl ammonium chloride),[69] TEBA (triethyl benzyl ammonium chloride)[70] and alumina[71] have been used for this preparation. However, most of these reported procedures have disadvantages including low yields, prolonged reaction times, use of an excess of reagents or catalysts, and use of toxic organic solvents. Therefore, an environmentally benign protocol for synthesis of 2,4,6-triarylpyridines is highly desirable.

We have developed a new an efficient, and green method for the synthesis of 2,4,6-triarylpyridines by one-pot three-component reaction of substituted acetophenones, aryl aldehydes, and ammonium acetate using CES as a natural solid base catalyst under aqueous conditions (Scheme 10). This procedure offers several advantages including mild reaction conditions, high yields, ease of workup, which makes it a useful and attractive protocol for the synthesis of these compounds. Furthermore, the catalyst obtained from renewable resources, could be recycled after a simple work-up, and reused at least six times with only slight reduction in its catalytic activity. It has also all advantages devoted to environmentally friendly conditions. The work in under process and we hope this work will be accepted in reputed journal in future.
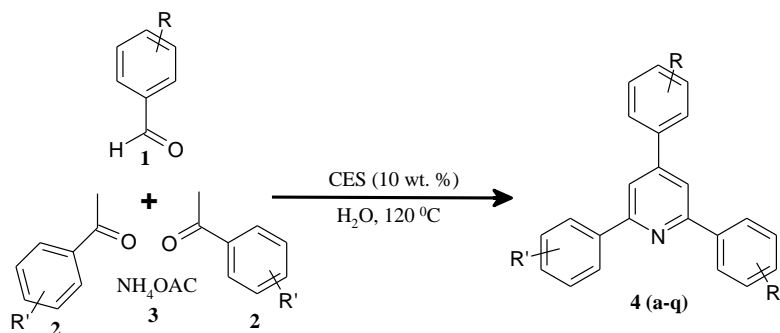

Scheme 10: synthesis of 2,4,6-triarylpyridines

Failure Reports:

Along-with the successful results, in some cases we got some failure results. Some of the important failure results are mentioned below.

Benzodiazopines are one of the important heterocyclic moieties. Despite their importance from a pharmacological, industrial and synthetic point of view, we have planned to synthesize benzodiazepine derivatives using lemon extract as acidic catalyst. However, no conversion of reactant into product was observed when o-phenylenediamine and ketones were reacted for longer reaction time in presence of lemon extract (Scheme 9).
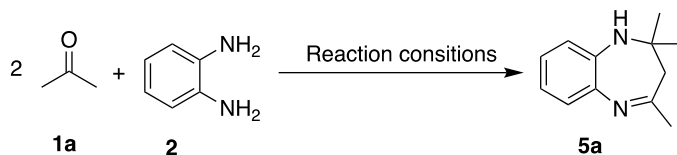
Scheme 9: Standard reaction of o-phenylenediamine and ketones reactants.

The pyranopyrazole moiety represents a fascinating template in the pharmaceutical field and is responsible for the wide spectrum of biological activities of molecules containing this significant unit. Such compounds can act as antidepressant, hypotensive, hypoglycemic, and anticancer agents. On the other hand, the pyranopyrimidine scaffold, as a key member of the pyrimidine family, has received considerable attention due to the broad range of antitumor, antibronchitic, hepatoprotective, and pronounced antitubercular and antimicrobial activities. The significant biological activity of pyranopyrimidine derivatives is a result of their occurrence in the structures of various natural products.

Hence we decided to evaluate utilization of lemon extract as a catalyst for synthesis of pyrazolopyranopyrimidines through the four-component reaction of hydrazine hydrazine, ethyl acetoacetate, 4-chlorobenzaldehyde and barbituric acid, but we got multiple products for the transformation (Scheme 10).
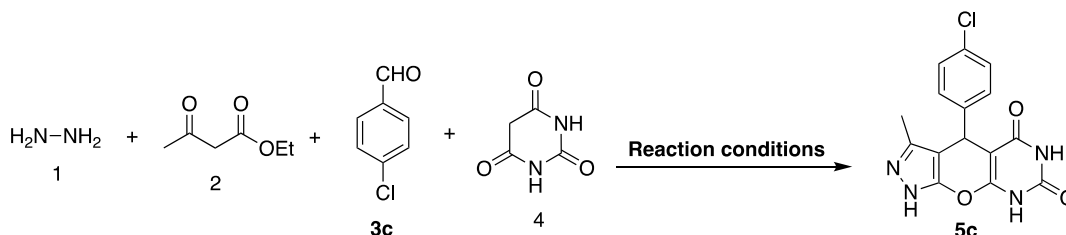
Scheme 10: Standard reaction of hydrazine hydrazine, ethyl acetoacetate, 4-chlorobenzaldehyde and barbituric acid reactants.

Our future plan is to overcome the difficulties arising in above failure results and to develop simple and efficient protocols to synthesize these important moieties using another natural sourced catalysts.

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