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Green methods for synthesis of various Heterocycles: Sustainable approach

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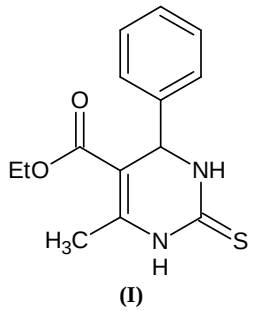
Abstract
Advancement of green chemistry carried out a number of challenges to those who applied chemistry in medicine industry, education and research. The start of green chemistry is considered as a revolution to the need to reduce the environment damage and human health risk by synthetic materials and the pathways used to made them. The preferable application of green chemistry in research is to utilize environment benign, mild, non toxic, reproducible catalyst and efficient solvents in synthesis of chemicals.

Keywords: Green chemistry, environment, green catalyst, chemical synthesis

1. Introduction
Today, chemistry plays a key role to improve and maintain our quality of life. The race of the chemical industry causes adverse effect on the natural environment and human health. In 1990 the US EPA (Environmantal Protection Agency) gives the term" Green Chemistry" to proceed chemical processes that eliminate the use of toxic or harmful substances in synthesis and manufacturing. The great profit came from pharma industries and research laboratories with design and synthesis of organic molecules. Green chemistry aims to eliminates the release of any hazardous bi-products and increase the yield of the target compound without spoil the environment. Paul Anastas and John C. Warner (1998) [1] states that green chemistry is the utilisation of a set of principles that reduces or eliminates the use of hazardous substances in the design of reaction mechanism, prevention of waste, maximize the atom economy, use of safer solvents, reduce derivatization and design for energy efficiency.

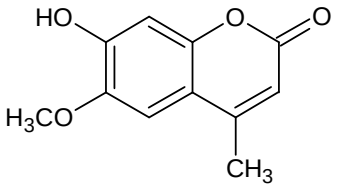
2. Green synthesis of some bioactive heterocyclic compounds by using different techniques and biocatalyst
Heterocyclic compounds are those compounds which contain at least different atoms other than carbon. Heterocyclic compounds represent the major class of bioactive organic compounds. Target of green chemistry is to overcome the negative environmental effects due to various hazardous chemicals used in synthetic pathways. The following examples shows a vast use of green chemistry in synthesis of heterocyclic compounds.

2.1 Using grinding method
Bose *et al,* 2004 reported the synthesis of ethyl 6-methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (I) with grinding technique by using Biginelli reaction. This method is simple, easy workup and environmentally benign.



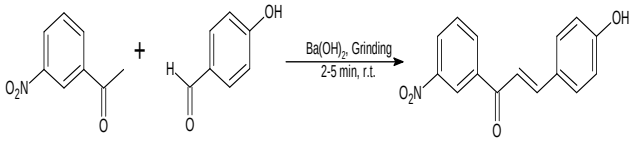
(I)

Jain *et al,* 2006 reported an environmentally benign synthesis of 7-hydroxy-6-methoxy-4-methyl-2H-chromen-2-one (II**)** by reaction between 3-hydroxy4-methoxyphenol and β keto ester by the Pechmann Reaction using grindstone techniques. This is an effort towards the energy efficient, eco-friendly synthesis of interesting organic molecules.



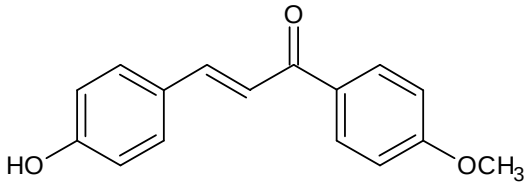
(II)

Kumar *et al.,* 2008 reported a simple, rapid, efficient green procedure for the synthesis of chalcones by grinding of aryl aldehyde and acetophenones with anhydrous barium hydroxide using C-200 in the absence of any solvent (Scheme-1).



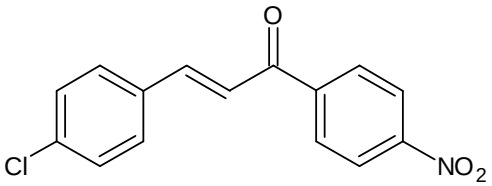
Scheme 1.

Rateb and Zohdi, 2009 [5] reported the reaction between substituted aldehyde and acetophenone to synthesize chalcone (2*E*)-3-(4-hydroxyphenyl)-1-(4-methoxyphenyl)prop-2-en-1-one (III) under solvent free condition with the help of grinding techniques. This method is very simple, economical, mild and environmentally benign as compared to classical reactions.



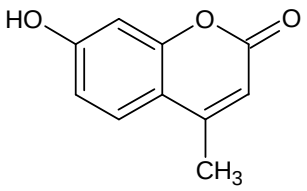
(III)

Zangade *et al,* 2011 [6] synthesized a novel chalcone (IV) in good yield. This compound was obtained by reaction between p-chloro benzaldehyde and p-nitro acetophenone. These synthesized compound shows antimicrobial activity. This method has been exhibited a unique advantages like no need of catalyst, ecofriendly, non toxic, use of safer and simple pathways.



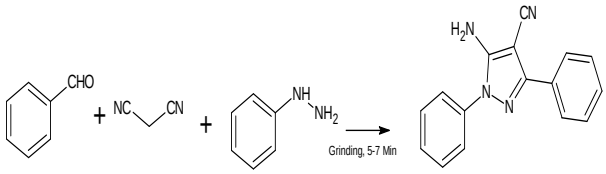
(IV)

Chavan *et al,* 2014 reported the synthesis of 7-hydroxy- 4-methyl coumarin (V) by using simple grinding technical method. They used an equimolar mixture of resorcinol and ethyl aceto acetate and add equimolar quantity of TsOH to this mixture in a mortar and ground it well with a pestle at room temperature.



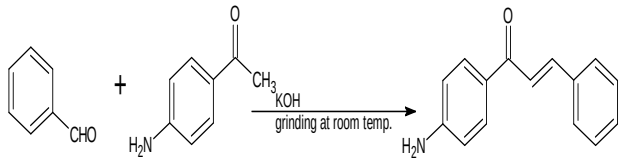
(V)

Bhale *et al*, 2014 [8] synthesized polysubstituted amino pyrazoles by simple grinding, catalyst free, one pot, three component system. This method showed that the most of the pyrazoles synthetic strategies involves multistep sequences, expensive catalyst, anhydrous conditions, inert atmosphere, long reaction time etc (Scheme -2).



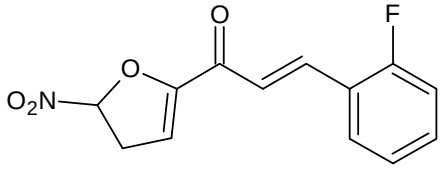
Scheme 2.

Shivshankar *et al,* 2016 [9] synthesized a novel chalcone under solvent free condition by using grinding method. This method is suitable in term of short reaction time, reaction procedure is very simple, no need of catalyst, attained better yield of product. This synthesized chalcones evaluated for their antioxidant activity (Scheme – 3).



Scheme 3.

Ali *et al,* 2016 [10] reported the environment friendly and efficient synthesis of chalcone derivative (VI) using solvent free technique by grinding different substituted benzaldehyde, acetophenone and NaOH pellets at room temperature. The reaction time needed to synthesize desired chalcones was 15-45 min.



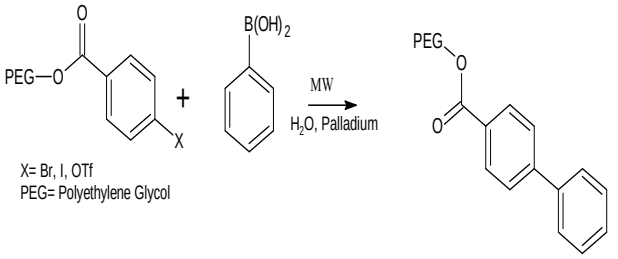
(VI)

2.2 Using microwave assisted organic synthesis

Synthesis of organic compounds were occurred by using microwave assisted technique. This method gives a notable advantages as compared to grinding and conventional method like reduction in reaction time, high yield, more atom

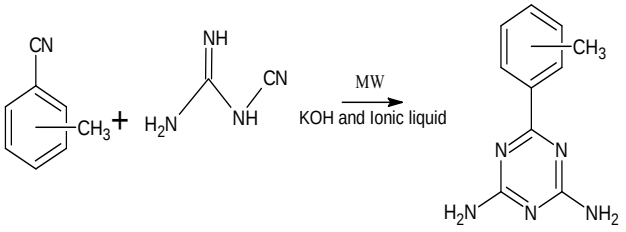
economy. This technique is more ecofriendly and provides an important approach towards green chemistry (Dasi *et al*., 2012) [11].

Lew *et al*., 2002 [12] synthesised highly fluorinated compounds on solid phase PEG. This is a safe reaction with microwave assisted and PEG is a soluble polymeric support for small molecule synthesis and provides easy purification after reaction (Scheme – 4).



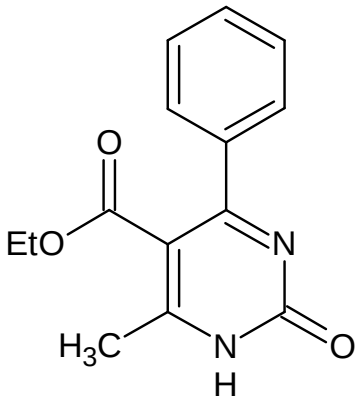
Scheme 4

Peng and Song 2004 [13] reported the synthesis of 4H-pyrans derivative under microwave irradiation by reacting 1-methyl-3-(2-aminoethyl) imidazolium hexafluorophosphate and water. Both of these are recyclable reaction medium and provides a ecofriendly pathways (Scheme - 5).



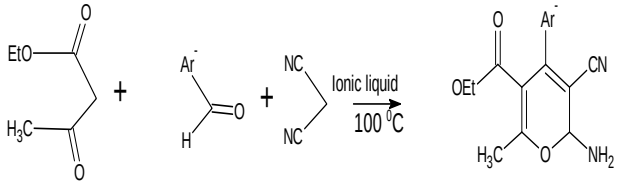
Scheme 5

Hakala *et al*, 2006 [14] reported a ionic liquid phase in organic synthesis protocol for the preparation of ethyl 6-methyl-2-oxo-4-phenyl-1,2-dihydropyridine-5-carboxylate (VII). Preparation of these compound occurred under microwave assisted techniques by using solvent free condition which is very environment benign.



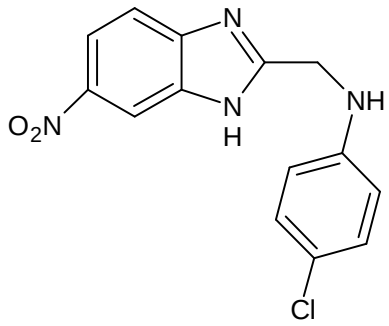
(VII)

Peng and Song 2007 [15] reported a microwave assisted synthesis of 6-aryl-2,4-diamino-1,3,5-triazines by reacting with aryl nitriles and cynoguanidines. This method is simple, efficient and ecofriendly (Scheme - 6).



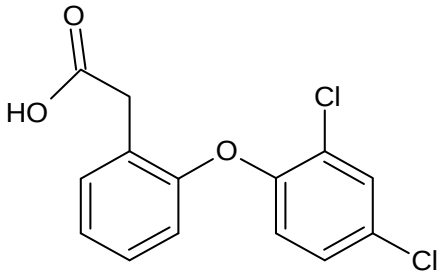
Scheme - 6

Bica *et al*., 2007 [16] described another procedure for synthesis of 4-chloro-*N*-[(6-nitro-1*H*-benzimidazol-2-yl)methyl]aniline an imidazolium chiral compound (VIII) with good yield of products. Microwave-assisted synthesis were used in the synthesis of these organic compounds which act as a very useful solvents in the Diels-Alder reaction with a proper diastereoselectivities.



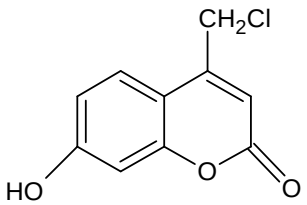
(VIII)

Savjani *et al*., 2010 [17] reported microwave assisted synthesis of Fenclofenac (IX) which is non-steroidal and anti-inflammatory in nature. This reaction takes very small time (1.5hour), good yield (52%) and environmentally mild as compared with conventional method. Conventionally synthesis of this compound has been undertaken in 3 steps pathway which takes 5 days in completion and final yield is very low (31%).

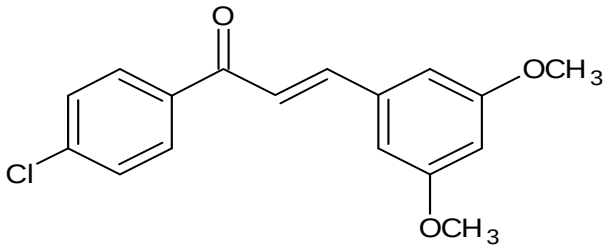


(IX)

Lucas *et al*, 2012 [18] reported an eco- friendly microwave assisted organic synthesis of coumarin (X) and chalcone (XI) derivatives under suzuki cross-coupling conditions by using PEG polyethyleneglycol as a solvent.

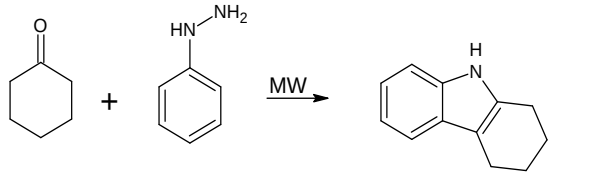


(X)



(XI)

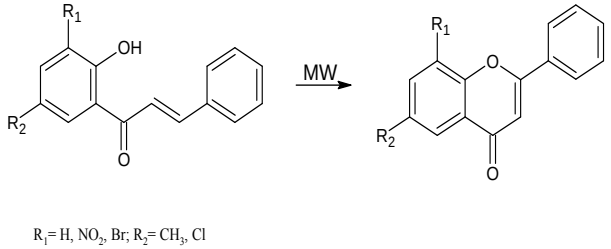
Nerkar *et al*., 2013 [19] reported the synthesis of tetrahydrocarbazole, by using microwave assisted chemical synthesis which is safer, faster and mild approach as compared to traditional pathways (Scheme-7).



1,2,3,4-tetrahydrocarbazole

Scheme 7

Sayre and Raguwanshi 2016 [20] reported a green pathway for synthesis of flavones by using microwave irradiation. Microwave synthesis shows advantage over conventional heating by time, extent of chemicals used and by yield. This method reduce the chemical wastage and more convenient than other reported methods (Scheme - 8).

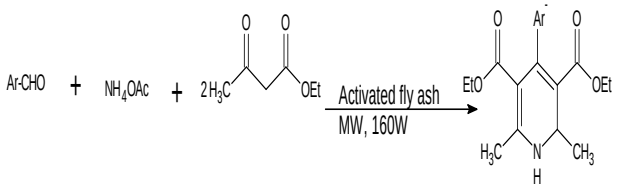


R_1= H, NO_2, Br; R_2= CH_3, Cl

Scheme 8

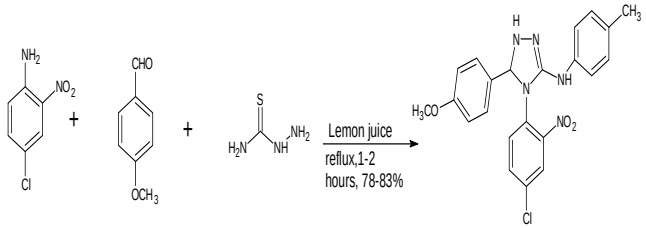
2.3 Using Green catalyst

Gopalkrishnan *et al.,* 2006 [21] reported a simplified green chemistry approaches to organic synthesis in solid media. Activated fly ash, an industrial waste which is an efficient and mild catalyst for some selected organic reactions in solvent-free conditions under microwave irradiation (Scheme – 9).



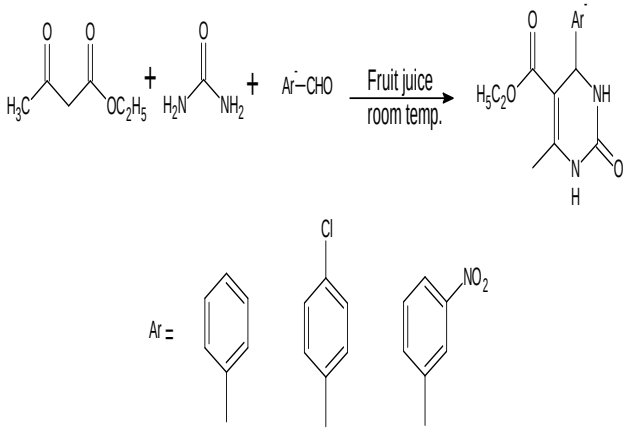
Scheme 9.

Sachdeva *et al*., 2013 [22] reported the multi-component synthesis of substituted -2H-1,2,3-triazoles derivatives using lemon juice in ethanol by the reaction of 4-chloro-2-nitro aniline and 4-methoxy aldehyde with thiosemicarbazide in maximum yield. They found that lemon juice plays a role of biocatalyst which provides a non hazardous and mild conditions which are basic principle of green chemistry (Scheme-10).



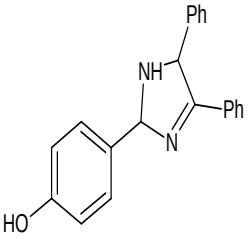
Scheme 10

Dihydropyrimidinone have been synthesized by Patil *et al*, 2011 [23]. These derivatives synthesized by using extract of lemon juice by reacting aldehydes, 1,3-dicarbonyl compounds with urea at room temperature under solvent free conditions. This is a one-pot multi-component system reaction where lemon juice acts as a green catalyst (Scheme - 11).

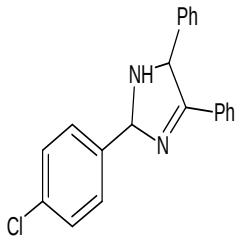


Scheme 11

Maske and Makhija, 2013 [24] synthesized trisubstituted imidazoles (XII) and (XIII) by using papain (papaya latex) which is an inexpensive, mild and nontoxic biocatatalyst. They perform the multicomponent synthesis from benzil, ammonium acetate and aromatic aldehyde in one pot.

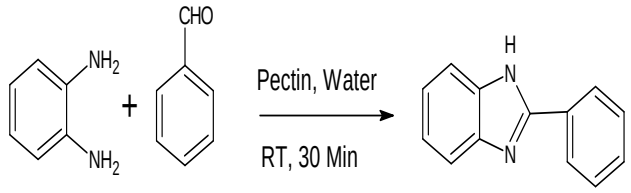


(XII)



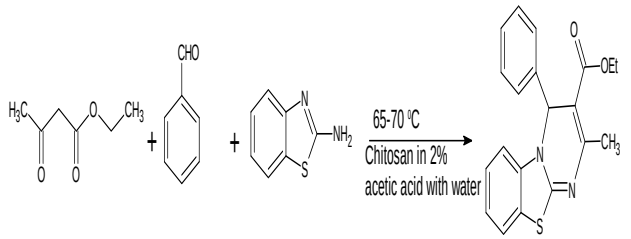
(XIII)

Agarwal *et al*., 2014 [25, 26] reported a mild and environmentally benign synthesis of Benzimidazole in excellent yield by using pectin as a green catalyst which is reusabale, time and energy saving, green method. (Scheme - 12).



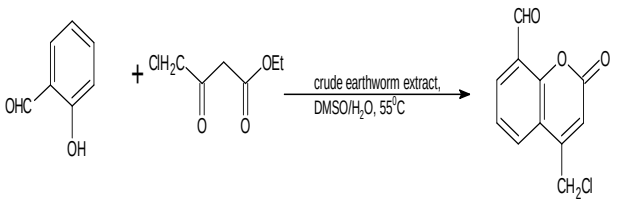
Scheme 12.

Sahu *et al.,* 2014 [26] reported the synthesis of 4H-pyrimido [2,1-b] benzothiazole derivatives by using an efficient, reusable and biodegradable biocatalyst. This is a multicomponent reaction of substituted aromatic aldehydes dicarbonyl and 2-aminobenzothiazole/3-amino-1,2,4-triazole/urea/thiourea in 2% acetic acid in aqueous media with chitosan as green catalyst at 60-65 ºC temp (Scheme - 13).



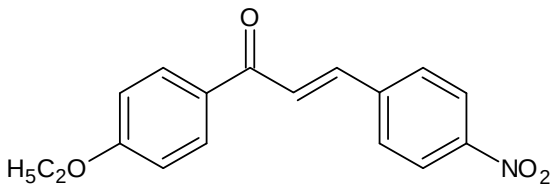
Scheme 13

Guan *et al*., 2014 [27] synthesized coumarin derivatives by the reaction of various salicaldehyde derivatives with different β-ketoesters in the presence of crude earthworm extract. They reported that various coumarin derivatives were obtained in yields of 32-87% in DMSO/Water. The main advantages of using the crude earthworm extract as a catalyst are ecofriendly, environmentally benign, safe cheap, easily accessible and stable (Scheme - 14).



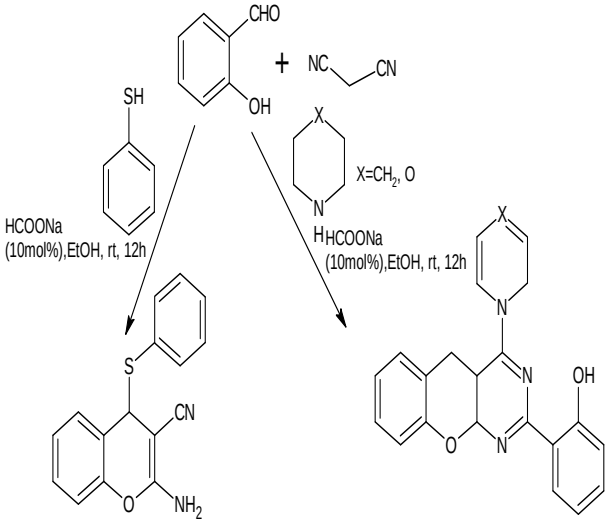
Scheme 14

Ezhilarasi *et al*., 2015 [28] designed a green chemical methods for the preparation of (2*E*)-1-(4-ethoxyphenyl)-3-(4-nitrophenyl) prop-2-en-1-one chalcone derivative (XIV) by using Amberlite Resin as an anion exchange medium. Chalcones are well known intermediates for synthesis of a large series of heterocyclic compounds. The product is easier to recover and the resin is reusable without loss of activity.



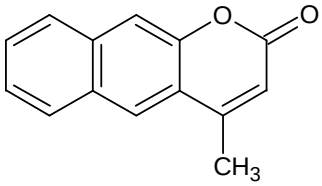
(XIV)

Brahmachari G, 2015 [29] synthesized 4H-pyrans and 4H-pyran annulated heterocycles by using sodium formate which is ecofriendly, cheap, easily available and non-toxic chemical substance. This pathway satisfies a number of green chemistry requirements (Scheme - 15).



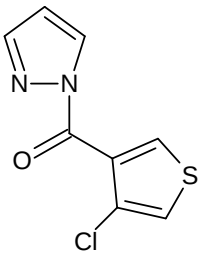
Scheme 15

Hussien *et al*., 2016 [30] synthesized coumarin derivatives (XV) via Pechmann condensation using naphthol and β-ketoester in presence of Amberlyst-15 which act as a green and reusable catalyst. They also found that coumarin derivative have biological activity and momentousness in the industrial fields.



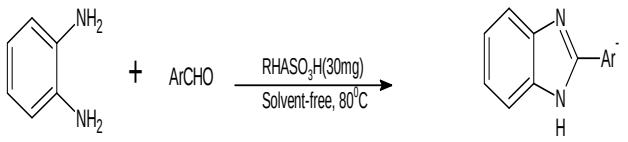
(XV)

Huang *et al*., 2016 [31] synthesized pyrano 2,3 pyrazoles (XVI) from one-pot four component system by using BSA as an effiicient and green biocatalyst. This catalyst could be used for five cycles without loss of catalytic activity.



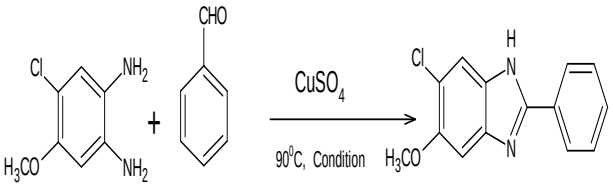
(XVI)

Sani *et al.,* 2016 [32] reported a green method for the preparation of benzimidazoles and quinoxalines by condensation of ortho-phenylenediamine with substituted aldehydes in presence of sulphonated rice husk (RHA-SO_3H). This method provides short reaction time and catalyst reusability (Scheme - 16).



Scheme 16

Karimi *et al*., 2016 [33] performs an easy, green, efficient and simple approach for synthesis of benzimidazole derivatives using Copper sulphate in aqueous media. This is a one-pot synthesis of biologically active benzimidazole derivatives under solvent free conditions (Scheme - 17).

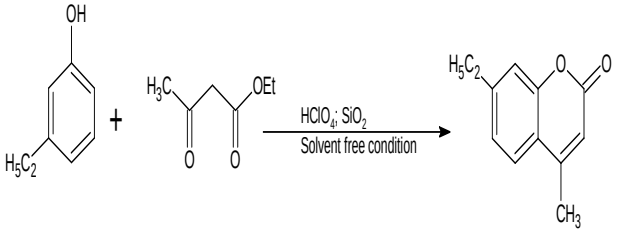


Scheme 17

2.4 Using solvent free conditions

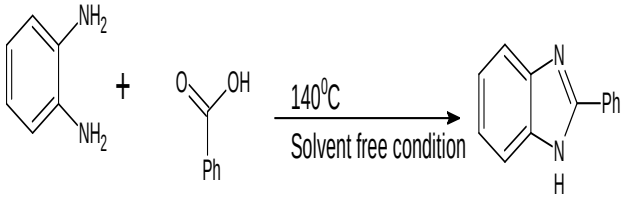
Most of the synthetic processes involve the use of different solvents. Unfortunately many of solvents are used in industry are volatile organic compounds which lead to environmental damage. Due to various advantage of solvent-free approaches are being discovered for ecofriendly synthesis of many compounds.

Maheswara *et al*, 2006 [34] reported the synthesis of substituted coumarins under solvent free conditions and by using heterogenous catalyst ($HClO_4$: SiO_2). This method provides a cost effective idea and benefits from the elimination of production of acidic waste (Scheme - 18).



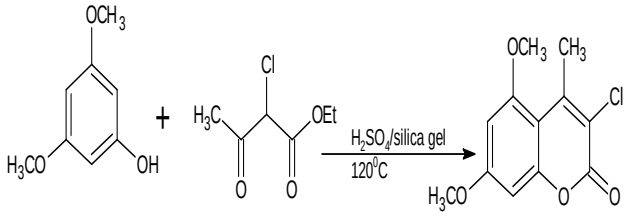
Scheme 18

Thakuria and Das 2008 [35] reported an expenditious one-pot solvent free synthesis of benzimidazole derivatives. Benzimidazole and its derivatives shows various biological activities like anti-viral, anti fungal, anti-cancer and anti-histaminic (Scheme - 19).



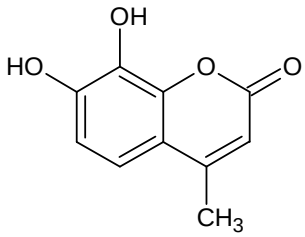
Scheme 19.

Reddy *et al*, 2009 [36] reported one-pot synthesis of coumarin catayzed by silica gel supported sulphuric acid under solvent free conditions. This method provides a green pathway for synthesis of coumarin by avoiding toxic catalyst and solvents (Scheme - 20).



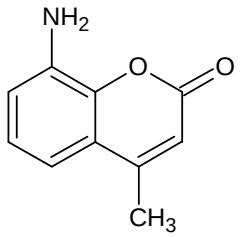
Scheme 20.

Rangappa *et al*, 2009 [37] reported a solvent free synthesis of coumarin derivatives **(XVII)** by using phosphotungstic acid as a catalyst. This is an efficient, facile and environmentally acceptable synthetic pathway in organic synthesis.



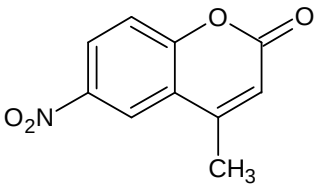
(XVII)

Khodabakhshi 2012 [38] synthesized 8-amino-4-methyl-2*H*-chromen-2-one coumarin derivative **(XVIII)** by using barium dichloride ($BaCl_2$) via pechmann condensation reaction without using any solvent. This method has advantages such as short reaction time, excellent yield of product and solvent free conditions in agreement with green chemistry principles.



(XVIII)

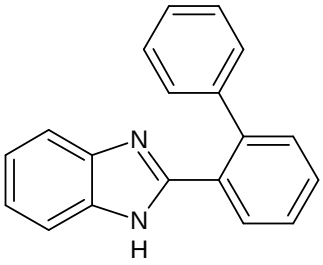
V. Vahibi and F. Hatamjafari 2014 [39] reported a rapid and efficient solvent-free, one pot synthesis of 4-methyl-6-nitro-2*H*-chromen-2-one coumarin derivative **(XIX)** by using FeF_3 as a catalyst. The synthesized products will show the antimicrobial activity.



(XIX)

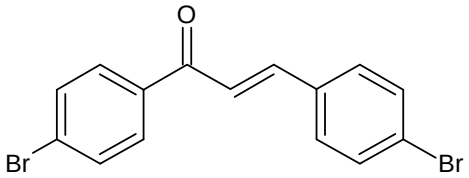
Habibi *et al*, 2015 [40] described a green and efficient synthesis of 2- aryl benzimidazoles **(XX)** by reaction between arylidene malanonitrile and 1,2-phenylenediammine derivatives in

solvent free conditions. This method shows simplicity of the reaction, good yield easy work up and product isolation.



(XX)

Muthuvel *et al*, 2016 [41] synthesized chalcone derivative (2*E*)-1,3-bis(4-bromophenyl)prop-2-en-1-one **(XXI)** by cross Aldol condensation of aryl methyl ketones using $FeCl_3$/ bentonite under solvent free conditions. They, found that this method provides a non hazardous, easy work up, shorter reaction time and better yields.



(XXI)

3. Conclusion

Green chemistry is the need of today and light of future which gives a precious idea for the scientifically based environmental protection. Chemists, researchers and pharmaceutical companies must be use to consider the principles of green chemistry while designing the reaction mechanism and selecting catalyst. By applying green chemistry procedures, we can minimize the waste materials, reduce the use of toxic chemicals, maintain the atom economy and save the environment which is heritage of our next generation.

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