

# One-pot Multi-component Synthesis of Some Pharmacologically Significant 2,4,5-Tri and 1,2,4,5-Tetrasubstituted Imidazoles: A Review

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## Authors' contributions

*This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.*

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## ABSTRACT

Heterocyclic compounds are acquiring more importance in recent years because of their pharmacological activities. Compounds containing imidazole moiety have many pharmacological properties and play important role in biochemical processes. Imidazole is a natural compound which exists in many important natural molecules such as the amino acid histidine, vitamin B12, histamine, biotin and purines like adenine and guanine. Imidazole derivatives play significant roles in various pharmacological activities such as anticancer, antibacterial, antifungal, antiviral, anti-HIV and antitubercular. This article aims to review the work in the methods of synthesis using various catalytic system, solvent condition and pharmacological potential of 2,4,5-tri and 1,2,4,5-tetrasubstituted imidazoles reported during last 15 years.

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## 1. INTRODUCTION

The chemistry of imidazole units is very important due to their potent biological activity and synthetic utilities. The potency and wide applicability of the imidazole pharmacophore can be attributed to its hydrogen bond donor-acceptor capability as well as its high affinity for metals, present in many protein active sites. [1] Appropriately substituted imidazoles are extensively used as glucagon receptors [2] and cannabinoid receptor antagonists [3], modulators of P-glycoprotein (P-gp) mediated multidrug resistance (MDR) [4], anti-tumour [5], antibacterial [6] and anti-inflammatory agents. These can also be utilized as fungicides [7] and plant growth regulators [8].

The research and development of imidazole-based chemistry have become a rapidly developing and increasingly active topic, towards their feasible applications in diverse areas, such as medicinal drugs, agrochemicals, man-made materials, artificial acceptors, supra molecular ligands and biomimetic catalysts [9-12]. Numerous imidazole-based compounds have playing a vital role in the treatment of various types of diseases and encouraged medicinal chemists to synthesize a large number of novel chemotherapeutic agents [13-15].

In recent years, alkylated imidazoliums have been used as ionic liquids [16] providing an approach to the 'Green Chemistry' protocol. The imidazole compounds have also been used in photography as photosensitive compounds [17].

Thus the main intention of this report is to survey the methods reported in the literature up to 2016 for the synthesis of tri- and tetrasubstituted 1*H*-imidazoles. In addition, this review outlines and discusses the biological activities of these heterocycles to make it more useful for medicinal chemists, pharmacists and pharmacologists.

## 2. MULTICOMPONENT REACTIONS

Multi-component reactions (MCRs) are convergent reactions, in which three or more starting materials react to form a product, where basically all or most of the atoms contribute to the newly formed product [18]. In an MCR, a product is assembled according to a cascade of elementary chemical reactions. Thus, there is a

network of reaction equilibria, which finally flow into an irreversible step yielding the product. The challenge is to conduct an MCR in such a way that the network of pre-equilibrated reactions channel into the main product and do not yield side products. The result is clearly dependent on the reaction conditions: solvent, temperature, catalyst, concentration, the kind of starting materials and functional groups. Such considerations are of particular importance in connection with the design and discovery of novel MCRs [19].

In the drug discovery process, MCR offers many advantages over traditional approaches. With only a limited number of chemists and technicians, more scaffold synthesis programs can be achieved within a shorter time. With one-pot reactions, each synthesis procedure (weighing of reagents, addition of reagents, reaction time, control) and work-up procedure (quenching, extraction, distillation, chromatography, weighing, and analysis) needs to be performed only once, in contrast to multi-step synthesis. MCRs are compatible with a solution phase approach, thus enabling a simple monitoring and they are easily amenable to automation. Moreover, each scaffold is expandable from a low number of compounds (scouting library) to a larger library. Thus, "hit-to-lead" transitions are normally accomplished easily and promptly. Certain physicochemical properties can be built into a library, e.g. lipophilicity and aqueous solubility, molecular weight, numbers of hydrogen donors and acceptors and the number of rotatable bonds, as well as the polar surface area. Finally, scale-up is often possible from a preclinical lab-scale (mg, gram) to clinical exploratory amounts (kg) using the same type of chemistry [20]. Drug molecules derived from MCR are very cost effective which, is the need of the hour.

MCRs have received considerable attention because of the complexity of the molecules that can be easily achieved from readily available starting materials in one reaction sequence [21]. MCRs generally occur in one pot and exhibit high atom economy and product selectivity. In most of the cases, they yield a single product and thus MCRs are advantageous over linear stepwise synthesis because of operational simplicity, reduction in reaction time, ecological friendliness, saving of money and raw materials, inexpensive

purification, and avoidance of protection and deprotection processes [22].

### 3. SYNTHESIS OF 1,2,4,5-TETRA AND 2,4,5-TRISUBSTITUTED IMIDAZOLES VIA ONE-POT MULTI-COMPONENT REACTIONS

The development of new MCRs with a variety of catalyst is an interesting area of current research. Owing to the wide range of pharmacological and biological activities, the synthesis of various imidazoles and their derivatives are important targets in current years, among these tri- and tetra substituted imidazoles have received much attention [23]. Several methods have been reported in literature exploiting the utility of MCRs.

2,4,5-trisubstituted imidazoles are generally synthesized by three component cyclocondensation of a 1,2-diketone, hydroxyketone or ketomonoxime with an aldehyde and ammonium acetate, which comprises the use of ionic liquids, [24] refluxing in acetic acid, [25] silica sulfuric acid [26]. On the other hand, the synthesis of 1,2,4,5-tetrasubstituted imidazoles have been carried out by four component condensation of a 1,2-diketone, hydroxy ketone or keto monoxime with an aldehyde, primary amine and ammonium acetate using microwaves, [27] heteropolyacid, [28] silica gel/NaHSO<sub>4</sub> [29] or HClO<sub>4</sub>-SiO<sub>2</sub> [30]. hetero-Cope rearrangement, [31] condensation of a 1,2-diketone with an aryl nitrile and primary amine under microwave irradiation [32].

Sharma et al. [33] have reported the InCl<sub>3</sub>.3H<sub>2</sub>O a mild and effective catalyst for the efficient, one-pot, three-component synthesis of 2,4,5-trisubstituted imidazoles at room temperature. Moreover, the utility of this protocol was further explored conveniently for the one-pot, four-component synthesis of 1,2,4,5-tetrasubstituted imidazoles in high yield (Scheme 1).

A simple, highly versatile and efficient synthesis of 2,4,5-trisubstituted imidazoles by three component cyclocondensation of 1,2-dicarbonyl compound, aldehyde and ammonium acetate using L-proline as a catalyst in methanol have been reported by Samai et al. [34] To explore the utility of this method 1,2,4,5-tetrasubstituted imidazoles were also synthesized with key advantages of the process as high yields, cost effectiveness of catalyst and purification of products by non-chromatographic methods.

Teimouri et al. [35] have reported a simple highly versatile and efficient synthesis of 2,4,5-trisubstituted imidazoles by three component cyclocondensation of 1,2-dicarbonyl compounds, aldehydes and NH<sub>4</sub>OAc, as ammonia source using clays, zeolite, nano-crystalline sulfated zirconia (S,Z) as catalyst. This protocol was explored conveniently for the one-pot, four component synthesis of 1,2,4,5-tetrasubstituted imidazoles in high yields with recovery and reuse of catalysts without any appreciable loss of their efficiency. Ziarani et al. [36] have reported SiO<sub>2</sub>-Pr-SO<sub>3</sub>H as a catalyst for the synthesis of 1,2,4,5-tetrasubstituted imidazoles by reaction of 1,2-diketones, aryl aldehydes, ammonium acetate and substituted aromatic amines under solvent-free conditions. An efficient and one-pot method for preparation of tri and tetra-substituted imidazoles by condensation of benzil, aldehydes and ammonium acetate or primary amine in the presence of a catalytic amount of citric acid or poly(4-vinylpyridiniumtribromide) (PVPBr<sub>3</sub>) under solvent-free condition has been reported by Ghorbani et al. [37] with remarkable advantages like inexpensive green catalyst, mild reaction conditions and excellent yields of product. The ZnO as an efficient and reusable catalyst have been used for the synthesis of substituted imidazole derivatives by Bahrami et al. [38] with a simple procedure and excellent yield.

Kumar et al. [39] have reported a robust and reliable one-pot multi-component method for the synthesis of 2,4,5-tri and 1,2,4,5-tetrasubstituted imidazoles, catalyzed by *p*-toluene sulfonic acid (PTSA), which provided good isolated yields under mild condition.

Karami et al. [40] have reported an efficient, easy, rapid and environmentally adapted synthesis of polysubstituted imidazoles *via* one-pot multi-component reaction of various aldehydes, benzil, aliphatic/aromatic primary amines and ammonium acetate under solvent-free condition with highly efficient role of yttrium nitrate hexahydrate {Y(NO<sub>3</sub>)<sub>3</sub>.6H<sub>2</sub>O} as catalyst. One-pot multi-component, synthesis of some novel environmental friendly poly substituted imidazoles also have been reported by Karami et al. [41] using various aldehydes, benzil, aliphatic/aromatic primary amines and ammonium acetate in the presence of Fe<sub>3</sub>O<sub>4</sub> nanoparticles as catalyst under solvent-free condition. Poorali et al. [42] have reported a new, efficient and environmental friendly synthesis of polysubstituted imidazoles *via* one-pot multi-component reaction of various aldehydes, benzil,

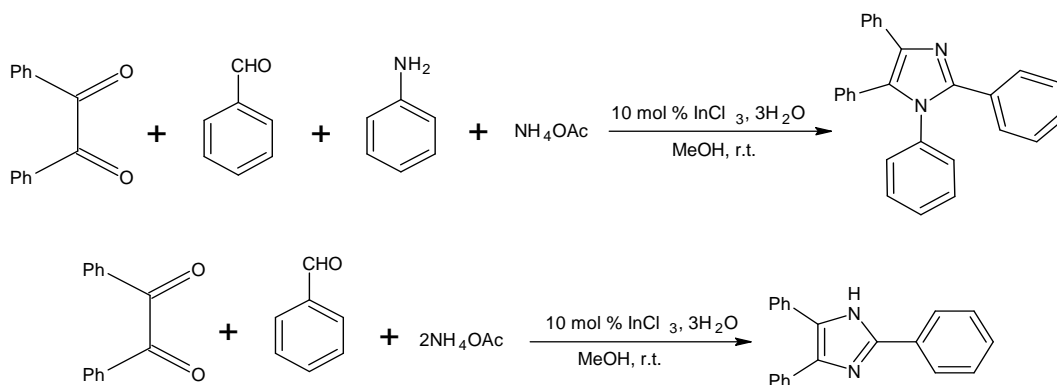
aliphatic/aromatic primary amines and ammonium acetate under solvent-free conditions highlighting the role of antimony trichloride and stannous chloride dihydrate as catalyst showing the effects on the reaction process.

It has been reported by Rostamnia et al. [43] that an adduct of unfunctionalized mesoporous SBA-15 and 2,2,2-trifluoroethanol SBA-15/TFE (Santa Barbara Amorphous) act as a catalyst for the reaction of aldehyde, amine and ammonium acetate with benzil to provide an entry in the synthesis of highly substituted imidazole derivatives with synthetic potential and a pharmaceutically interesting compound *via* one-pot multi-component method which carried the advantages of being performed under the neutral conditions and required no activation or modification of the substrates. Borhade and co-workers [44] have reported an one-pot synthesis of 2,4,5-tri and 1,2,4,5-tetrasubstituted imidazoles under solvent-free conditions using nanocrystalline silica supported tin oxide ( $\text{SiO}_2\text{:SnO}_2$ ) as catalyst. Ramesh et al. [45] have reported the synthesis of 2,4,5-tri and 1,2,4,5-tetrasubstituted imidazoles using a new

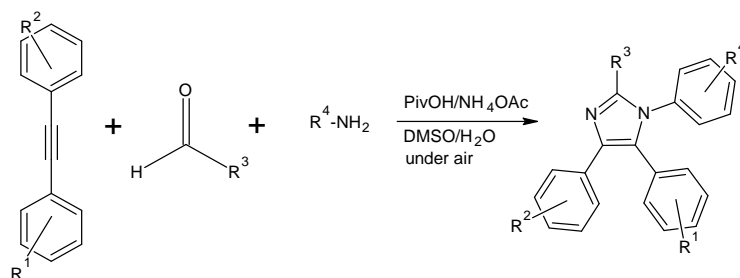
bioglycerol-based carbon catalyst *via* the reaction of aromatic aldehyde, ammonium acetate/amine and 1,2-diketone in acetonitrile. Karimi Jaber et al. [46] have reported sodium dihydrogen phosphate ( $\text{NaH}_2\text{PO}_4$ ) catalyzing efficiently the condensation of benzil, aldehydes, amines and ammonium acetate in the synthesis of 2,4,5-tri and 1,2,4,5-tetra-substituted imidazoles.

Chen et al. [47] have developed an expedient metal-free synthetic route for the construction of 2,4,5-tri and 1,2,4,5-tetra-substituted imidazoles derivatives *via* acid-promoted MCR methodology. The reaction proceeded smoothly with a range of functionalities to produce the imidazole scaffolds in good to excellent yields (Scheme 2).

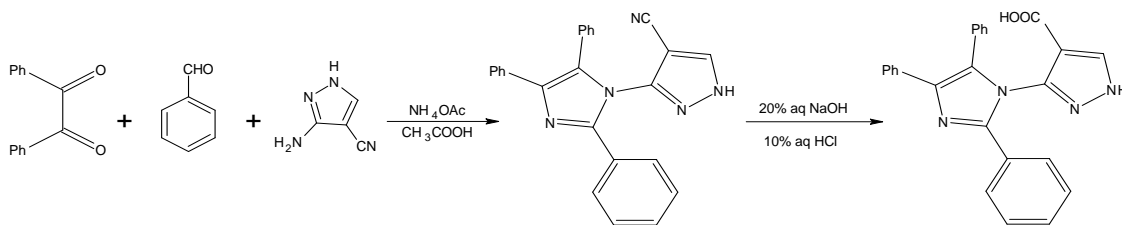
Sridharan et al. [48] have reported an elegant synthesis of novel 1-pyrazole acid triphenyl imidazoles by the cyclization of benzil with aromatic aldehydes in the presence of ammonium acetate and amino pyrazole to give 1-cyanopyrazole-2-substitutedphenyl-4,5-diphenyl-imidazole followed by acid hydrolysis (Scheme 3).



Scheme 1



Scheme 2



**Scheme 3**

Maleki et al. [49] have achieved a highly versatile and efficient synthesis of 2,4,5-trisubstituted imidazoles by three-component cyclocondensation of 1,2-dicarbonyl compounds, aldehydes and  $\text{NH}_4\text{OAc}$  as ammonia source using urea/hydrogen peroxide (UHP) as a supported green catalyst in refluxing ethanol (Scheme 4).

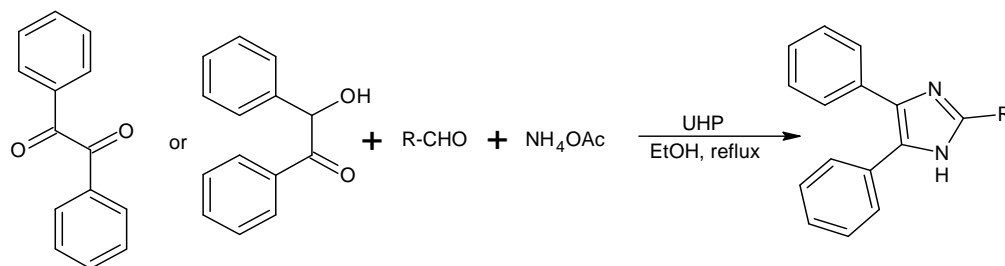
Maske et al. [50] have developed a reliable method for the synthesis of 2,4,5-trisubstituted imidazole from benzil, ammonium acetate and aromatic aldehyde using papain a non toxic and inexpensive catalyst (Scheme 5).

Marzouk et al. [51] have reported morphonium hydrogen sulphate as Brønsted acid ionic liquid an efficient and reusable catalyst for the one-pot synthesis of 2,4,5-trisubstituted imidazoles *via* cyclocondensation of 1,2-dicarbonyl compound, aromatic/aliphatic aldehyde and ammonium acetate. This process was proved advantageous in view of cost effectiveness, reusability of

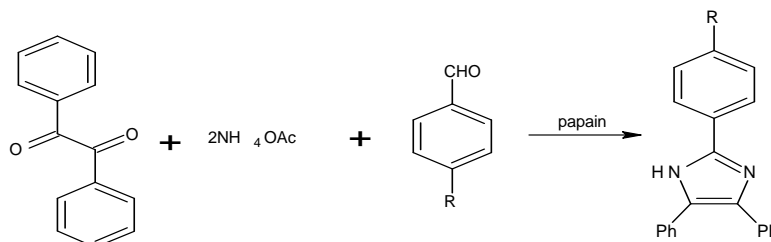
catalyst, purification of products, excellent yields and very short time of reaction (Scheme 6).

The new results concerning synthesis of some 2,4,5-triaryl-1*H*-imidazoles in the absence of any additive as catalyst were presented by Tayeb et al. [52] (Scheme 7).

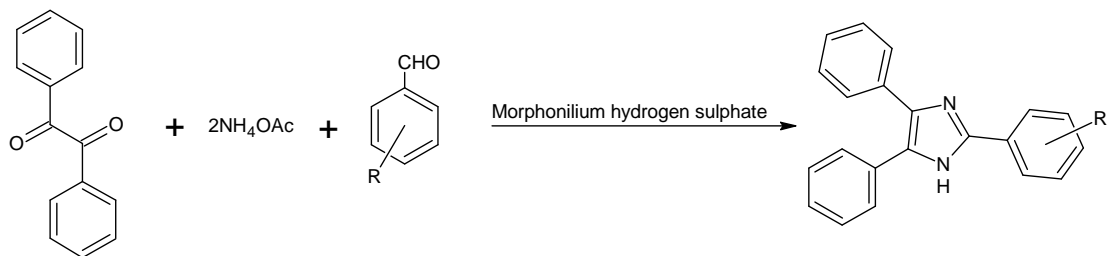
An efficient and advantages process in a view of high yields, cost effectiveness of catalyst, easy work-up and purification of products 2,4,5-trisubstituted imidazoles cyclocondensation of 1,2-dicarbonyl compound, aldehyde and ammonium acetate using ammoniumchloride ( $\text{NH}_4\text{Cl}$ ) as a catalyst has been reported by Maleki et al. [53]. Qasim et al. [54] synthesized 2-phenylimidazo[1,10]phenanthroline derivatives by reacting dicarbonyl compound and *p*-substituted benzaldehydes by the acid catalyzed 1-methyl-3-heptylimidazolium tetrafluoroborate  $[(\text{HeMIM}) \text{BF}_4]$ , under solvent-free, environmental friendly reaction and microwave assisted conditions with easy work-up and better yields (Scheme 8).



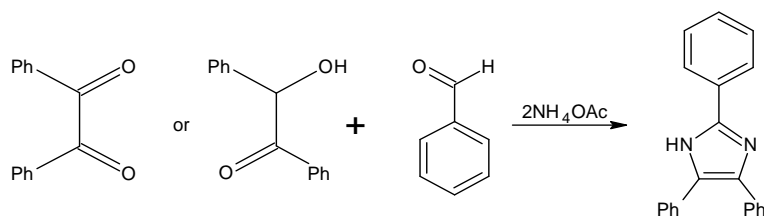
**Scheme 4**



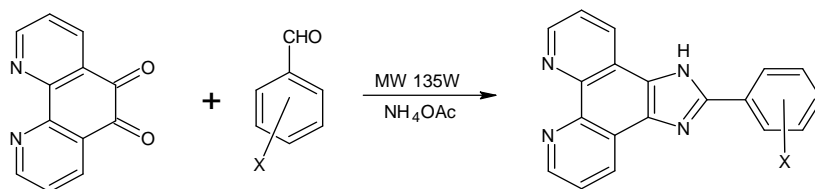
**Scheme 5**



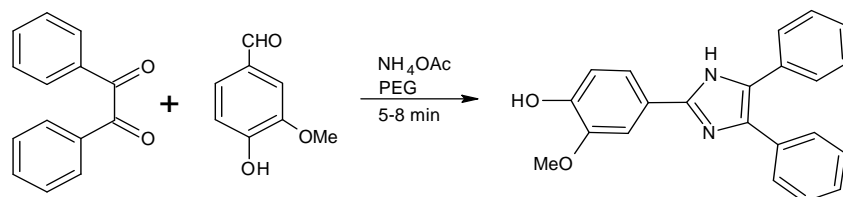
Scheme 6



Scheme 7



Scheme 8



Scheme 9

Nalage et al. [55] have developed an efficient and green method for the synthesis of 2,4,6-triaryl-1-*H*-imidazole in poly ethyleneglycol (PEG) which is non toxic, reusable, inexpensive and easily available, by condensing benzil and 3-methoxy-4-hydroxybenzaldehyde under micro wave irradiation in excellent yields (Scheme 9).

A novel urea-functionalized silica based magnetic hybrid nanoparticle with a core-shell structure was prepared by Maleki et al. [56] founding to be a highly efficient and recoverable heterogeneous nanocatalyst for the three-component condensation reaction between benzil or benzoin with various substituted

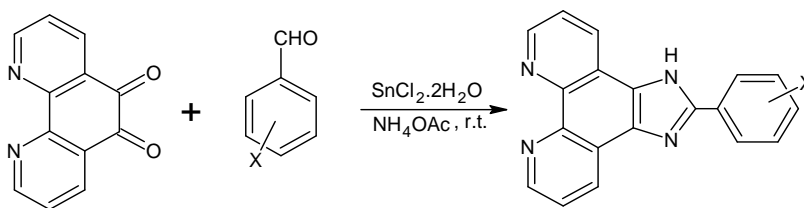
aldehydes and ammonium acetate to afford the corresponding imidazoles under mild conditions. This procedure offered many advantages including short reaction times, high quantitative yields, low cost and straightforward work-up. Qasim et al. [57] have reported the synthesis of various 2-phenylimidazo[4,5-*f*]phenanthrolines via  $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$  catalyzed three-component reaction of 1,10-phenanthroline-5,6-dione, aromatic aldehydes and ammonium acetate at room temperature in excellent isolated yields. This method was proved simple and straightforward without involving any hazardous or expensive catalyst (Scheme 10).

Gharib et al. [58] have reported one-pot multi-component synthesis of 2,4,5-tri and 1,2,4,5-tetrasubstituted-1*H*-imidazole derivatives by condensation of benzil or benzoin, aldehydes, ammonium acetate and primary amines under reflux using silica-supported Preyssler nanoparticles heteropolyacid as a catalyst (Scheme 11).

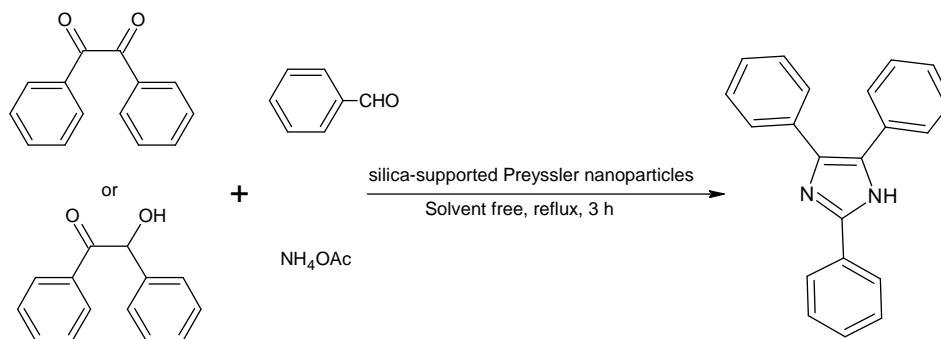
Nagargoie et al. [59] have reported a new user friendly one-pot procedure for the synthesis of 2-aryl-4,5-diphenyl-1*H*-imidazoles by the condensation reactions of benzil/benzoin, with aromatic aldehyde and ammonium acetate using diethyl bromophosphate (DEP) as a mild oxidant under

ultrasound (US) irradiation. The synthesis of imidazole derivatives by the reactions of 9,10-phenanthrene quinone/benzil using supported ionic liquid like phase (SILIP) as a green catalyst has been described by Jourshari et al. [60] under ultrasonic irradiation. The catalyst is easily separated from reaction mixture by filtration (Scheme 12).

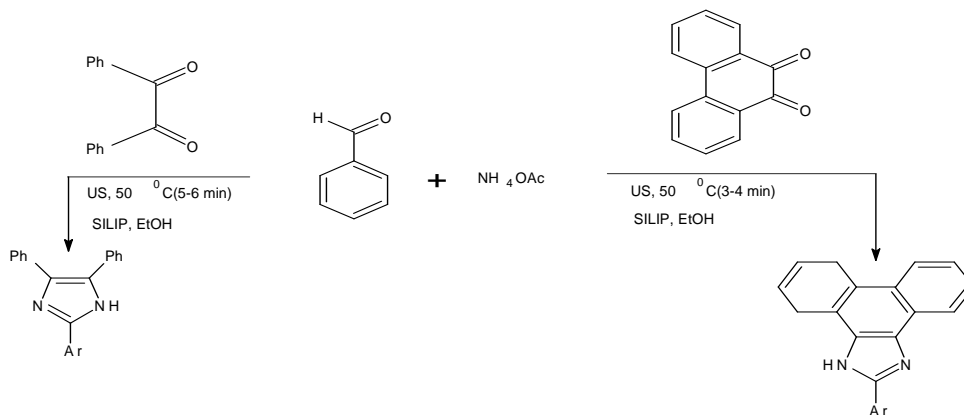
Bade et al. [61] have reported a one-pot, four-component synthesis of 1,2,4-trisubstituted imidazoles by reacting a mixture of bromoacetic acid, aromatic aldehyde, benzyl amine and ammonium acetate in dry alcohol (Scheme 13).



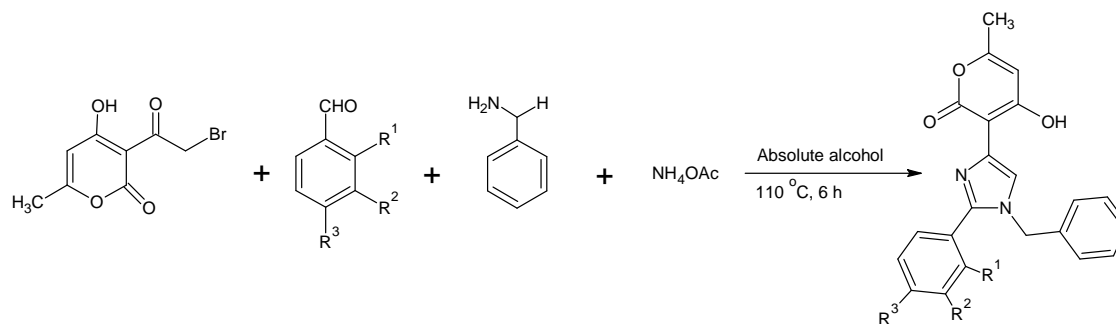
Scheme 10



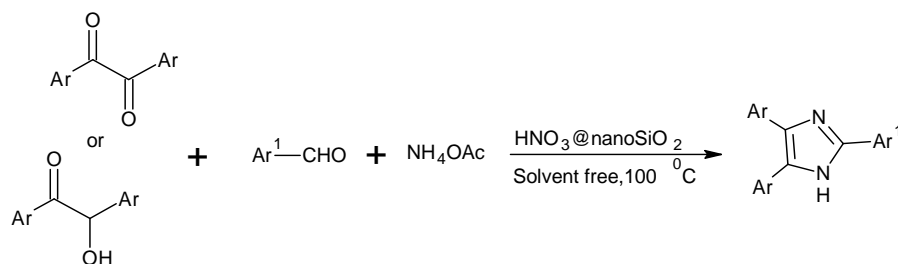
Scheme 11



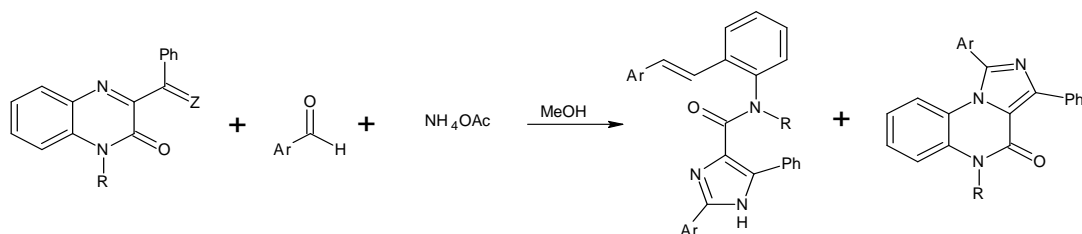
Scheme 12



Scheme 13



Scheme 14



Scheme 15

The synthesis of 2,4,5-trisubstituted imidazoles has been achieved by cyclocondensation of benzil or benzoin, an aldehyde and ammonium acetate using deep eutectic solvent (DES) of choline chloride and oxalic acid as a novel acidic catalyst by Bakavoli et al. [62]. Crucial advantages of this process was high yields, shorter reaction time, easy work-up, purification of products by non-chromatographic methods and reusability of the catalyst.

Nikoofar et al. [63] have synthesized concentrated nitric acid supported on nano silica ( $\text{HNO}_3@\text{nano SiO}_2$ ) via a simple procedure which has been utilized as an effective catalytic system for the synthesis of various 2,4,5-tri and 1,2,4,5-tetrasubstituted imidazoles under solvent-free conditions at 100°C. The recovery and reusability of  $\text{HNO}_3@\text{nano SiO}_2$  have been checked in 3 runs without activity loss. The

significant features of this acidic nano catalyst in the reported procedure are high yield of products, short reaction time and green reaction media (Scheme 14).

Mamedov et al. [64] have reported 3-arylquinoxalin-2(1H)-ones as hetero analogues of  $\alpha$ -diketones for the efficient, one-pot, three component synthesis of 2,4,5-trisubstituted imidazoles and imidazo[1,5-a]quinoxalin-4(5H)-ones in boiling methanol. The key advantages of this process were high yields, readily availability, low cost of 3-arylquinoxalin-2(1H)-ones, easy work-up and separation of the products by non chromatographic methods (Scheme 15).

Murthy et al. [65] have reported a simple and efficient protocol for the synthesis of highly substituted imidazoles through the condensation of 1,2-dicarbonyl compound, aldehyde and



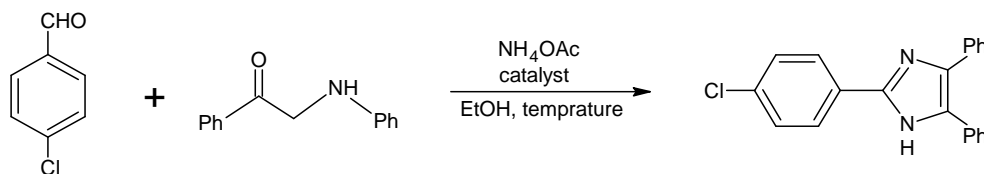
ammonium acetate or amine *via* multi-component condensation strategy which gave good to excellent yields. Rathinam et al. [66] have reported to achieve a simple, highly versatile and an efficient synthesis of 1,2,4,5-tetrasubstituted imidazoles by four-component cyclocondensation of benzil, aromatic aldehyde, aminoethylpiperazine and ammonium acetate using sulphated yttria ( $\text{SO}_4^{2-}/\text{Y}_2\text{O}_3$ ) as a catalyst in ethanol medium. An attractive synthetic protocol by the aspect of condensation in the presence of supported reagents with operational simplicity, inexpensive reagents, high yield of products and the use of non-toxic reagents have been reported by Sivakumar et al. [67] in which Cu(II) nitrate impregnated zeolite was used as an efficient reagent for rapid one-pot synthesis of 2,4,5-tri and 1,2,4,5-tetrasubstituted imidazoles with excellent yields. An operationally simple, metal-free and economical one-pot three-component cycloaddition reaction for the synthesis of 1,2,4-trisubstituted imidazoles using aldehydes,  $\alpha$ -amino carbonyl compounds and ammonium acetate has been developed successfully by Tang et al. [68] This environment friendly transformation by employing  $\text{I}_2$  (10 mol %) as a catalyst and EtOH as a solvent with wide range of functional groups and heterocycles giving rise from moderate to good yields (Scheme 16).

One step synthesis of silylated 1,2,4,5-tetraaryl imidazoles using a series of metal containing silicoaluminophosphate-34 (M/SAPO-34) (M: Fe, Co, Mn and Cu) nanocatalysts and subsequent silylation reactions were described by Safa et al. [69] Cu/SAPO-34 catalyst has been reported with highest activity in improving the efficiency of the heterogeneous cyclocondensation of an aldehyde, benzil, ammonium acetate and a primary aromatic amine in water under ultrasonic irradiation. An efficient and eco-friendly procedure for shorter reaction time, recyclable catalyst and excellent yields has been developed by Safari et al. [70] using nanocrystalline

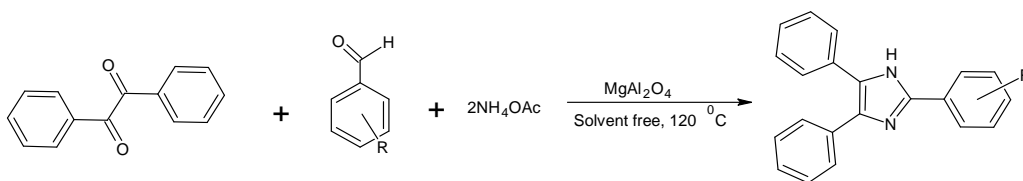
$\text{MgAl}_2\text{O}_4$  as catalyst for rapid and an improved synthesis of 2,4,5-tri and 1,2,4,5-tetrasubstituted imidazoles under solvent-free conditions (Scheme 17).

Some novel Lewis acids catalysts were prepared by sulfonated carbon/silica composites derived from starch and silica by the treatment with Lewis acids e.g.  $\text{AlCl}_3$ ,  $\text{SbCl}_3$ ,  $\text{Bi}(\text{NO}_3)_3$ ,  $\text{ZnCl}_2$  and  $\text{FeCl}_3$  have been reported by Gupta et al. [71]. The catalytic activity of these Lewis acids have been evaluated for one-pot synthesis of 1,2,4,5-tetrasubstituted imidazoles, 3,4-dihydropyrimidin-2(1*H*)-ones and for Michael addition of indole to  $\alpha$ ,  $\beta$ -unsaturated ketones. Sulfonated carbon/silica composite functionalized ( $\text{CSC-Star-SO}_3\text{-AlCl}_2$ ) Lewis acids were found as the most effective solid Lewis acid for the synthesis on investigation. An efficient, readily available and reusable silica supported boron trifluoride ( $\text{BF}_3\cdot\text{SiO}_2$ ) catalyst was prepared by a very simple procedure affording good to excellent yields in synthesizing 1,2,4,5-tetrasubstituted imidazoles by the use of benzil, aromatic aldehyde and an amine in the presence of ammonium acetate have been reported by Sadeghi et al. [72].

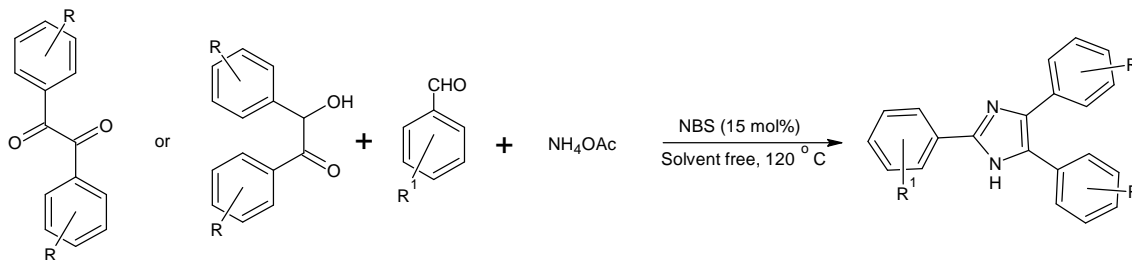
A simple and efficient method has been developed by Joshi et al. [73] which involved the smooth condensation of benzil/benzoin with substituted aldehydes and ammonium acetate in the presence of potassium dihydrogen phosphate ( $\text{KH}_2\text{PO}_4$ ) catalyst under mild conditions to afford 2,4,5-triaryl-1*H*-imidazoles. Ali et al. [74] also reported the design and synthesis of some tetra substituted imidazoles. An efficient protocol bearing advantages of good yields, less pollution and simple reaction conditions for the one-pot multi-component synthesis of various 2,4,5-triaryl-1*H*-imidazoles and 1,2,4,5-tetraaryl-1*H*-imidazoles using polyethylene glycol (PEG-400) as a reaction medium was described by Wang et al. [75].



Scheme 16



Scheme 17



Scheme 18

Samanta et al. [76] have reported an efficient and green method for the synthesis of 2,4,5-triaryl-1*H*-imidazoles without using any catalyst or solvent. The results concerning synthesis of some 2,4,5-triaryl-1*H*-imidazoles in absence of any catalyst have been reported by Tayebee et al. [77] and the experimental route for the isolation and purification of the un-reacted reactant at the end of the reaction was also modified. An interesting and alternative protocol of one-pot cyclocondensation of benzil, aldehydes, ammonium acetate and primary amines to synthesize 2,4,5-tri and 1,2,4,5-tetrasubstituted-1*H*-imidazole derivatives by the stable, highly active, easy preparation and handling silica-supported  $\text{SbCl}_3$  ( $\text{SbCl}_3/\text{SiO}_2$ ) heterogeneous catalyst under microwave irradiation have been reported by Safari et al. [78] which was eco-friendly and green from the environment stand-points.

Babu et al. [79] developed a simple and reliable synthetic method for 2,4,5-trisubstituted imidazoles by the condensation of benzil, ammonium acetate and various aromatic aldehyde in the presence of  $\text{ZrO}(\text{NO}_3)_2$  as a catalyst. This method has key advantages as solvent-free, purification of products by non-chromatographic methods, good yield and short reaction time. An efficient synthesis of 2,4,5-tri and 1,2,4,5-tetrasubstituted imidazoles by one-step condensation of aldehyde, benzil, ammonium acetate and primary amine in the presence of nano-crystalline magnesium aluminate under microwave irradiation have been described by Safari et al. [80].

A simple, green and efficient method with major advantages of high yields, less reaction times,

easy purification of the products, environmental friendliness and convenient operation for the synthesis of 2,4,5-triaryl-1*H*-imidazoles using *N*-bromosuccinimide (NBS) catalyst under solvent-free conditions have been reported by Maleki et al. [81] (Scheme 18).

Secondary amine based ionic liquid and defective Keggin type heteropolyacids (HPA) were separately used by Das et al. [82] for efficient one-pot four-component microwave assisted (MW), eco-friendly and solvent-free synthesis of 1,2,4,5-tetrasubstituted imidazoles bearing important features as short reaction time, high yield of products and reusability of catalysts. This work also demonstrated the alternate use of urea, instead of often used ammonium acetate, as source of nitrogen. Hasaninejad et al. [83] have reported a catalyst-free one-pot four-component methodology for the synthesis of 1,2,4,5-substituted imidazoles under conventional heating and microwave irradiations using 1-butyl-3-methylimidazolium bromide [Bmim]Br, as a neutral reaction media. In this procedure a broad range of structurally diverse aldehydes and primary amines were used successfully.

Moosavi-Zare et al. [84] have reported tritylchloride ( $\text{TrCl}$  or  $\text{Ph}_3\text{CCl}$ ) efficiently catalyzing one-pot multi-component condensation of benzil, aldehydes, primary amines and ammonium acetate under neutral and solvent-free conditions to give 1,2,4,5-tetrasubstituted imidazoles with high yields in short reaction times. Application of sulfuric acid immobilized on silica gel ( $\text{H}_2\text{SO}_4 \cdot \text{SiO}_2$ ) an efficient and benign catalyst has also been

explored to utilize in the synthesis of 2,4,5-triaryl-1*H*-imidazoles *via* condensation of benzil or benzoin, aldehyde and ammonium acetate [85] with high yields, cost effectiveness of catalyst, easy work-up, purification of products by non-chromatographic method and reusability of the catalyst.

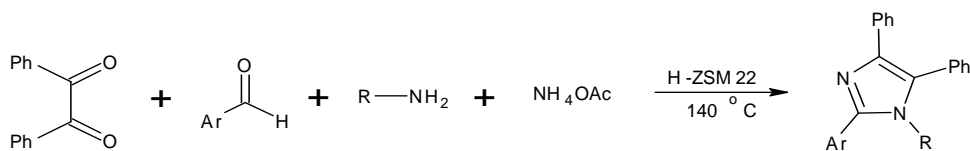
The use of a heterogeneous catalyst tetrabutylammoniumhexatungstate [TBA]<sub>2</sub>[W<sub>6</sub>O<sub>19</sub>] under thermal (140 °C), solvent-free conditions have been reported by Ashrafi et al. [86] for a simple and efficient synthesis of 2,4,5-trisubstituted imidazoles *via* one-pot three-component cyclocondensation of benzil, aromatic aldehydes and ammonium acetate. This methodology has been reported with key features of operational simplicity, high yields, short reaction times and recyclable catalyst with a very easy work-up. Vosoughi et al. [87] have reported a simple one-pot three-component synthetic method for 2,4,5-tri and 1,2,4,5-tetrasubstituted imidazoles by three-component cyclocondensation of benzil, aromatic aldehydes and ammonium acetate under solvent-free conditions in the presence of ZSM-5-SO<sub>3</sub>H as a catalyst.

An efficient Ho<sup>3+</sup> doped CoFe<sub>2</sub>O<sub>4</sub> nanoparticles catalyzed one-pot synthesis of 2,4,5-triaryl-1*H*-imidazoles has been developed by Pachpinde et al. [88] *via* three-component condensation of benzil or benzoin, aromatic aldehydes and ammonium acetate in ethanol as advantageous method due to little catalyst loading, short reaction time, reusability of catalyst and excellent yields. The use of ionic liquid 1-methyl-3-(3-trimethoxysilylpropyl)imidazoliumchloride immobilized on super paramagnetic Fe<sub>3</sub>O<sub>4</sub> nanoparticles (IL-MNPs) as an efficient heterogeneous catalyst for the synthesis of 1,2,4,5-tetrasubstituted imidazoles using microwave irradiation have been reported by Safari et al. [89] The combined microwave irradiation and immobilized ionic liquid on super paramagnetic nanoparticles made the four-component condensation with safe operation, low pollution, rapid access of products and simple work-up. Sondankar et al. [90] have reported an efficient and rapid synthesis of 2,4,5-triphenyl-1*H*-imidazole derivatives under solvent-free condition by the condensation of benzil, arylaldehyde and ammonium acetate at 110°C using zinc acetate as a catalyst.

Babu et al. [91] have reported a rapid, simple, efficient and environmentally benign synthesis of

1,2,4,5-tetrasubstituted imidazole under solvent-free condition catalyzed by ZrO(NO<sub>3</sub>)<sub>2</sub>.XH<sub>2</sub>O. The advantages of this method were as solvent-free, simple work-up, readily available catalyst, short reaction time and very good yield. Kantevari et al. [92] have reported a protocol for the synthesis of 1,2,4,5-tetrasubstituted imidazoles under solvent-free conditions using perchloric acid adsorbed on silica gel (HClO<sub>4</sub>-SiO<sub>2</sub>) as catalyst with remarkable catalytic activity in excellent yields. Chavan et al. [93] have developed an efficient solvent-free methodology for the synthesis of various 2,4,5-triaryl and 1,2,4,5-tetraaryl imidazoles offering several advantages of excellent yields, shorter reaction times and reusability of catalyst using silica chloride as a heterogeneous catalyst. Bhat et al. [94] have reported an environmentally benign, green and efficient catalyst zeolite H-ZSM-22 for an improved and rapid synthesis of 1,2,4,5-tetrasubstituted imidazole derivatives by condensation of benzil, aldehydes, amines and ammonium acetate with excellent yields (Scheme 19).

A simple, highly versatile and efficient three-component cyclocondensation of 1,2-dicarbonyl compounds, aldehydes and ammonium acetate resulted in the formation of 2,4,5-trisubstituted imidazoles by the use of Brønsted acid ionic liquid diethylammonium hydrogen phosphate catalyst. [95] Nasr-Esfahani et al. [96] have used nano-rod vanadatesulfuric acid (VSA NRs), as a recyclable and eco-benign catalyst for the synthesis of 2,4,5-tri and 1,2,4,5-tetrasubstituted imidazoles using benzil/benzoin or 9,10-phenanthrenequinone, aldehydes and ammonium acetate or aniline under solvent-free conditions. Wang et al. [97] have synthesized a non-toxic, cost effective and recyclable Brønsted acid deep eutectic solvent based on choline chloride and *p*-toluene sulfonic acid which was found to be effective for the one-pot synthesis of 2,4,5-tri and 1,2,4,5-tetrasubstituted imidazoles. Nikalje et al. [98] have described a facile, one-pot three-component synthesis of a series of 3[(4,5-diphenyl-2-substituted-aryl/heteryl)-1*H*-imidazol-1-yl]-1*H*-1,2,4-triazole-5-carboxylic acid derivatives using ceric ammonium nitrate (CAN) as a catalyst. Mirjalili et al. [99] have synthesized 2,4,5-trisubstituted imidazoles in the presence of trichloro melamine as a catalyst. Caro's acid-silica-gel [100] have been also found to be a mild and effective catalyst for the synthesis of 2,4,5-trisubstituted imidazole derivatives under solvent-free conditions. Sulfated MCM-41



Scheme 19

(Mobiloil Composition of Matter-41) as reusable, inexpensive, non-toxic and efficient heterogeneous catalyst [101] have been reported to utilized for an improved and rapid one-pot synthesis of 2,4,5-tri and 1,2,4,5-tetrasubstituted imidazoles. Tetra-butylammoniumbromide [102] (TBAB) have been reported as catalyst for the synthesis of highly substituted imidazoles *via* multi-component condensation of 1,2-diketone, aldehyde, amine and ammonium acetate. A protocol offering advantages in terms of higher yields, short reaction times, and mild reaction conditions, with reusability of the catalyst have been reported by Dandia et al. [103] as a facile and efficient synthesis of 2,4,5-triarylimidazoles achieved by employing three-component one-pot reaction using aromatic aldehydes, benzil and  $\text{NH}_4\text{OAc}$  in the presence of Co doped ZnS nanoparticles in water under ultrasonic irradiation. Bamoniri et al. [104] have reported a synthetic route for trisubstituted imidazoles using nano  $\text{SbCl}_5/\text{SiO}_2$  as catalyst under solvent-free conditions. This method has provided several advantages like simple work-up, environmentally benign, shorter reaction times and high yields.

Kalkhorani et al. [105] have reported an efficient method for the synthesis of 1,2,4,5-tetrasubstituted imidazoles using  $\text{K}_7\text{Na}_3\text{P}_2\text{W}_{18}\text{Cu}_4\text{O}_{68}$  as catalyst. Tahara et al. [106] have developed a solvent-free microwave-assisted synthesis of 2,4,5-tri and 1,2,4,5-tetrasubstituted imidazoles *via* the condensation of 1,2-dicarbonyl compounds with aldehyde and amine using solid support acidic alumina impregnated with ammonium acetate. Molecular iodine has been reported as a cheap, nontoxic and efficient catalyst in the synthesis of 1,2,4,5-tetraaryl imidazoles *via* the condensation of benzoin, aromatic aldehyde and amine in the presence of ammonium acetate by Kidwai et al. [107].

Maleki et al. [108] have described a green, rapid, convenient and eco-friendly method for the synthesis of 2,4,5-trisubstituted imidazoles in the presence of grapheneoxide-chitosan bio-nanocompo- site as an efficient nano-catalyst. Rajaguru et al. [109] have reported the synthesis of substituted imidazole derivatives from various

$\alpha$ -azido chalcones, aryl aldehydes and anilines. This multi-component protocol employed erbiumtriflate  $\{\text{Er}(\text{OTf})_3\}$  as a catalyst resulting in excellent yield. Keivanloo et al. [110] have reported Boehmite nanoparticles ( $\text{AlOOH NPs}$ ) as a highly active and green catalyst for the synthesis of highly substituted imidazoles under solvent-free conditions. Phosphorus pentoxide supported on silica gel ( $\text{P}_2\text{O}_5/\text{SiO}_2$ ) has been used as an efficient and reusable catalyst for the one-pot four-component synthesis of 2,4,5-tri and 1,2,4,5-tetrasubstituted imidazoles by Reza et al. [111]. The remarkable features of this procedure were as high conversions, cleaner reaction, simple procedures and easy separation of the catalyst.

Saghanezhad et al. [112] have reported one-pot preparation of 2,4,5-tri and 1,2,4,5-tetrasubstituted imidazoles in the presence of poly(4-vinylpyridiniumbutanesulfonic acid) hydrogensulfate P(4-VPBSA)-  $\text{HSO}_4$ , as an efficient dual acidic catalyst under solvent-free conditions. Reusability of the catalyst, easy work-up procedure, eco-friendly, short reaction times and high yields of the products illustrated the utility of this approach. Mohammad et al. [113] have reported an efficient method for synthesis of various tetrasubstituted imidazoles, using trifluoroacetic acid (TFA) as a catalyst by four-component condensation of benzil, aldehydes, amines and ammonium acetate under microwave-irradiation and solvent-free conditions. Hekmatshoar et al. [114] have reported 2-ethylhexanoic acid as a dual solvent-catalyst for the one-pot, four-component synthesis of 1,2,4,5-tetrasubstituted imidazoles. This naturally occurring and widely produced fatty acid exhibited remarkable catalytic activity which was easily separated by extraction. The reusability of this catalytic medium was tested by recovering the catalyst and using it again in the reaction up to four times with no significant drop in activity. The catalyst is commercially available, low cost and eco-friendly, offering short reaction times, good to excellent yields and a straightforward work-up procedure.

Sanasi et al. [115] have reported a simple, one-pot multi-component method for the synthesis of

poly substituted imidazoles in the presence of magnetically separable and recyclable spinel nanocopper ferrite as heterogeneous catalyst by the condensation of benzil, aromatic aldehyde, ammonium acetate and substituted amines under ultrasonic irradiation. This methodology offered simple experimental procedure, milder reaction conditions and environmentally benign approach. Parveen et al. [116] have reported synthesis of 2,4,5-triaryl substituted imidazoles in very good yields under solvent-free conditions by grinding 1,2-diketones, aromatic aldehydes and ammonium acetate in the presence of molecular iodine as catalyst. The short reaction time, cleaner reaction and easy work-up make this protocol practical and economically attractive. Girish et al. [117] have reported synthesis of 2,4,5-trisubstituted imidazoles and 1,2-disubstituted benzimidazoles by ZrO<sub>2</sub>-supported- $\beta$ -cyclodextrin (ZrO<sub>2</sub>- $\beta$ -CD) under solvent-free conditions. Sharma et al. [118] have reported a reliable synthesis method for 2,4,5-trisubstituted imidazole from benzil, ammonium acetate and aromatic aldehyde using BiCl<sub>3</sub> as a catalyst in solvent CH<sub>3</sub>CN.

Gelens et al. [119] have reported the four-component synthesis of 2,4,5-tri and 1,2,4,5-tetrasubstituted imidazoles employing a microwave-assisted protocol. Raghuvanshi et al. [120] have synthesized a series of 1,2,4,5-tetrasubstituted imidazoles by one-pot condensation of benzil, aromatic aldehyde, aliphatic/aromatic amine and ammonium acetate using Fe<sup>3+</sup>-K10 a heterogeneous catalyst under solvent-free microwave conditions. Ya et al. [121] have reported solvent-free microwave-assisted synthesis of 2,4,5-tri and 1,2,4,5-tetrasubstituted imidazoles by condensation of 1,2-dicarbonyl compounds with aldehyde and amine (aliphatic/aromatic) with ammonium acetate using acidic alumina impregnated as the solid support. Shapi et al. [122] have reported one-pot synthesis of 2,4,5-triaryl imidazoles at room temperature using 1-butylimidazoliumtetrafluoroborate ([Hbim]BF<sub>4</sub>) ionic liquid as a catalyst. Zolfigol et al. [123] have reported one-pot four-component synthesis of 1,2,4,5-tetrasubstituted imidazoles by condensation reaction of benzil/benzoin, aldehydes, amine derivatives and ammonium acetate at room temperature under solvent-free conditions using 2,6-dimethylpyridiniumtrinitro methanide {[2,6DMPyH]C(NO<sub>2</sub>)<sub>3</sub>} a novel and efficient catalyst as nanostructured molten salt. Sharekh et al. [124] have reported the synthesis of 2,4,5-triaryl-1*H*-imidazoles by condensation of benzoin, aromatic aldehyde and ammonium

acetate using SO<sub>4</sub><sup>2-</sup>/CeO<sub>2</sub>-ZrO<sub>2</sub> solid acid as a catalyst in ethanol.

#### 4. PHARMACOLOGICAL PROFILE OF IMIDAZOLES

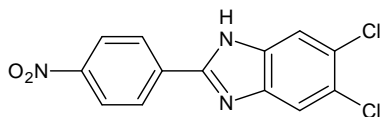
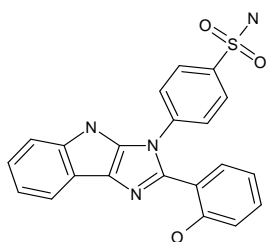
Multi-substituted imidazoles an important class of pharmaceutical compounds [125-127] exhibit a wide spectrum of biological activities such as analgesic, [128] anti-convulsant, [129] anti-inflammatory, [130] anti-parasitic, [131] antifungal, [132] antidepressant, [133] anti-tubercular, [134] anti-allergic, [135] antibacterial, [136] anti-tumour [137] and antiviral activities [138] as well as anti-leishmanial activity against *Leshmania donovani*. [139] Furthermore they can act as inhibitors of p38MAP-kinase [140] and glucagon receptors [141]. Due to the resistance of some microorganisms to imidazole action because of outer membrane modifications, development of new and different antimicrobial agents has been becomes a prime objective of medicinal and synthetic chemists. Therefore much of the current research efforts are oriented toward the design of new and readily available drugs [142-144].

Over the years the imidazole nucleus has attracted the attention of the scientific community due to its chemical and biological properties [145] e.g. nucleus is present in the structures of several natural products in the form of the essential amino-acid histidine or in alkaloids exhibiting anti-tumour, anti-cancer (dacarbazine), antihistaminic (cimetidine), anti-parasitic (metronidazole), and antihypertensive (losartan) and anti-bacterial activities [146-148]. A great numbers of medicines containing the imidazole nucleus, including ketoconazole have used to treat gastric ulcers, fungal and bacterial infections [149,150].

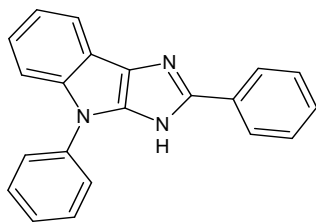
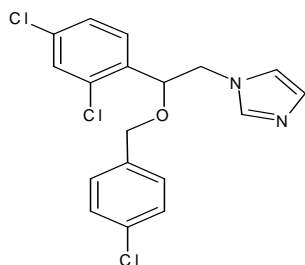
Imidazoles have many applications in pharmacological and biochemical development [151] e.g. the hypnotic agent (etomidate), [152] the proton push inhibitor (omeprazole) [153] and the benzodiazepine antagonist (flumazenil) [154] are imidazole derivatives. For all above applications the synthesis of imidazoles has become very vital objective in present duration. 2,4,5-triaryl-1*H*-imidazole is harmful towards human life also for animal because it reduces platelet aggregation in some animal and humans.

Tonelli and co-workers have synthesized a series of 2-phenylbenzimidazole derivatives and evaluated them for cytotoxicity and antiviral

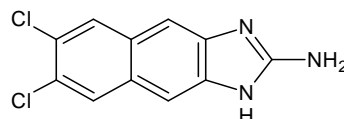
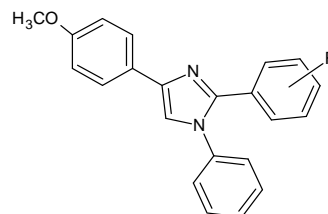
activity against a panel of RNA and DNA viruses. Compound 5,6-dichloro-2-(4-nitrophenyl)-1-*H*-benzimidazole (**1**) exhibited higher activity than reference drug [155]. Prabhu and co-workers have reported the synthesis of 4-[2-(2-hydroxyphenyl)imidazo[4,5-*b*]indol-3(4*H*)-yl]benzene-sulfonamide (**2**) which exhibits good anti-bacterial and anthelmintic activity [156].

**(1)****(2)**

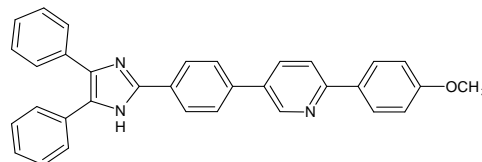
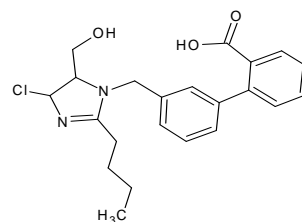
A series of 2,4-diphenyl-3,4-dihydroimidazo[4,5-*b*]indole (**3**) synthesized by Bhargava and co-workers have been reported exhibiting good anticonvulsant activity [157]. Wyler and co-workers have synthesized a series of 1-[2-[(4-chlorobenzyl)oxy]-2-(2,4-dichlorophenyl)ethyl]-1-*H*-imidazoles (**4**) and tested their antifungal activity [158].

**(3)****(4)**

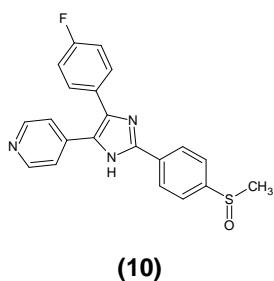
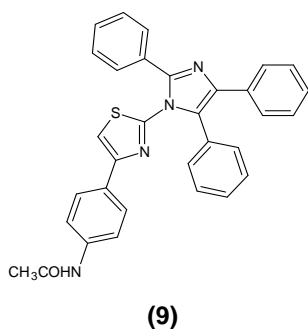
Li and co-workers have reported a series of 1-(4-phenyl-1,3-thiazol-2-yl)-4-(Thienyl-2-yl)-1-*H*-imidazol-2-amine having good anticancer activity [159]. Bender et al. have also reported 4,5-bis(4-methoxyphenyl)-2-(trifluoromethyl)-1-*H*-imidazoles showing good analgesic and anti-inflammatory activity [160]. Zhu and co-workers have synthesized a series of 6,7-dichloro-1-*H*-naphtho[2,3-*d*]imidazol-2-amine (**5**) and evaluated their antiviral activity [161]. Husain et al. have synthesized-(4-methoxyphenyl)-1,2-diphenyl-1-*H*-imidazoles (**6**) and found exhibiting anti-inflammatory and antifungal activities [162].

**(5)****(6)**

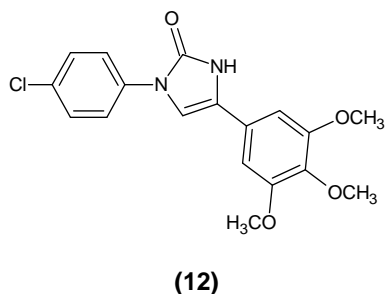
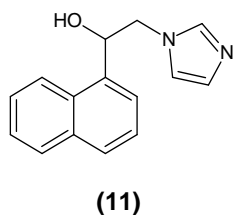
Nagarajan et al. reported a series of 5-[4-(4,5-diphenyl-1-*H*-imidazol-2-yl)-phenyl]-2-(4-methoxyphenyl)pyridines (**7**) with antibacterial and antifungal activities [163]. 3'-(2-butyl-4-chloro-5-(hydroxymethyl)-4,5-dihydro-1-*H*-imidazol-1-yl)methyl)-[1,1'-biphenyl]-2-carboxylic acids (**8**) have been found to showing good antifungal activity by Shreenivas and co-workers [164].

**(7)****(8)**

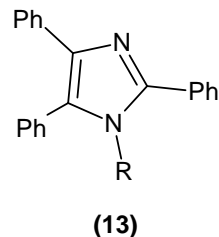
Sharma and co-workers have reported the synthesis and anticancer activities [165] of 4-(2-(2,4,5-triphenyl-1*H*-imidazol-1-yl)thiazol-4-yl)phenylacetamides (**9**). Adams and co-workers have reported the synthesis of 4-{4-(4-fluorophenyl)-2-[4-(methylsulfinyl)phenyl]-1*H*-imidazol-5-yl}pyridine (**10**) and found them with anti-inflammatory activity [166].



Walker and co-workers have synthesized a series of 2-(1*H*-imidazol-1-yl)-1-(Naphthyl-1-yl) ethanol (**11**) compounds with anticonvulsant activity [167]. Narasimhan and co-workers have synthesized a series of 1-(4-chlorophenyl)-4-(3,4,5-trimethoxyphenyl)-1,3-dihydro-2*H*-imidazol-2-one (**12**) which were found to show good anticancer activity [168].



A series of 1-substituted 2,4,5-triphenyl imidazoles (**13**) were synthesized by Yashoda et al. [169] and screened for mild to moderate anti-inflammatory and antimicrobial activities.

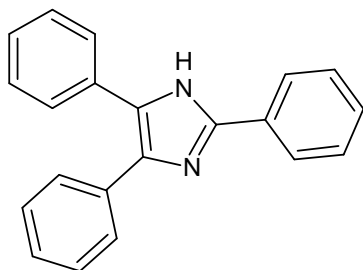


Many drugs have imidazole nucleus in their structure have been found in medicinal field like dacarbazine as anticancer, metronidazole as antifungal, cimetidine as anti-histamics and flumazenil as benzodiazepine antagonist [170]. Imidazole-containing antifungal drug (ketoconazole) was also found to have anti-inflammatory activity in addition to its antifungal activity [171]. Flutrimazole another imidazole-based wide spectrum antifungal agent was found to be a good topical anti-inflammatory agent [172]. Therefore, imidazole nucleus seems to be an important pharmacophore for designing of new drug candidates.

A new series of 1,2,4-trisubstituted nitrogen heterocycles acting as inhibitors of transforming expansion factor  $\beta$  type-1 receptor (ALK5) were synthesized by Li and co-workers [173]. Husain and co-workers described anti-inflammatory and antimicrobial activities of tri-substituted imidazoles [174]. A series of novel 1,2,4-trisubstituted-1*H*-imidazole derivatives with anticonvulsant activity were synthesized by Husain et al. [175]. The preparation of several new 1,2,4-trisubstituted imidazoles and 1-(benzo[1,3]dioxol-5-yl)-2-(6-methylpyridin-2-yl)-4-substituted imidazoles containing a methylene amino linkage on the 4-position of the core ring were reported [176] some of them act as inhibitors of transforming expansion factor- $\beta$  type-I receptor (ALK5). Umarani and co-workers demonstrated an elegant procedure for the preparation of several diverse N,N-disubstituted-2,4,5-triphenyl-1*H*-imidazole-1-yl-methanamine hybrids [177] and *in-vitro* anti-inflammatory, antibacterial and antifungal activities. It was found that some of them showed good anti-inflammatory potency and better antimicrobial activity against bacterial strains; *Staphylococcus aureus*, *Pseudomonas aeruginosa* and fungal strain; *Candida albicans*. Anti-inflammatory screening revealed that all the synthesized

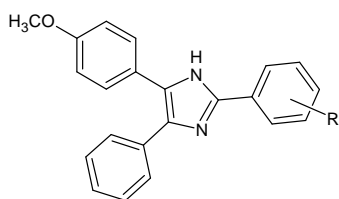
moieties were remarkably potent in comparison with the well-known and prescribed drug diclofenac sodium. Heterocyclic compounds having 2,4,5-tri and 1,2,4,5-tetra-substituted imidazoles in their structures possess a versatile range of pharmacological activities. Some of them were used as anti-inflammatory agents, [178] several act as kinase inhibitors [179].

Jain et al. [180] have synthesized 2-substituted-4,5-diphenyl-*N*-alkylimidazoles and evaluate their antibacterial activity. All the synthesized compounds were evaluated for antibacterial activity against *S. aureus*, *B. subtilis*, and *E. coli* the results showed some short of activity but none of them had considerable activity compared with that of the standard. 4,5-triphenyl-1*H*-imidazole-1-yl derivatives (**14**) have been synthesized and tested for their anti-inflammatory activity *in-vitro* using phenylbutazone as a reference drug and antimicrobial activity using clotrimazole and ciprofloxacin as a standard drug by Shailesh et al. [181].



(14)

Ambadkar et al. [182] have reported the preparation of 2-(Substitutedphenyl)-4-(4-methoxyphenyl)-5-phenyl-1*H*-imidazole (**15**) by the condensation 4-methoxybenzil, substituted benzaldehyde and ammonium acetate in glacial acetic acid as a solvent. The synthesized compounds have been evaluated for their antimicrobial activity using Gram positive and Gram negative bacteria and found to be more potent antimicrobial drugs.



(15)

## 5. CONCLUSION

MCRs are a useful class of reactions for never ending hunt for biologically active compounds and complementarily add into the large arsenal of tools available to the modern chemists. The literature survey reveals that great biological potential and easy routes for synthesis of imidazoles have attracted the attention of chemists, pharmacologists and researchers. The therapeutically active moiety 2,4,5-tri and 1,2,4,5-tetrasubstituted imidazoles had been exploited in the recent past for the synthesis of various pharmacologically active compounds. By the present scenario it can be concluded that imidazoles have a great potential for further research and novel derivatives can be synthesized containing this core fragment and can be explored for various biological activities.

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## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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