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*RESEARCH ARTICLE*

# DIVERSE SYNTHETIC APPROACHES TO CRAFT IMIDAZOLES - A REVIEW

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## *Abstract*

Imidazoles are five membered heterocyclic ring compounds containing two nitrogen atoms as a part of a five membered ring. Imidazole is a pharmacologically important molecule mainly used as antihypertensive, antiplasmodial, antifungal and anticancer agents etc. It can be synthesized by using a variety of starting materials by different synthesis such as – Debus Radziszewski, Van Leusen, Wallach synthesis to name a few. By altering the starting materials different derivatives of imidazole can be synthesized and show a wide range of pharmacological activites. Hence organic chemists are continuously striving to synthesize novel imidazole derivatives that could show better pharmacological effects. This review article focuses on different types of synthesis available to chemists for this versatile molecule.



## Introduction: -

Planar, amphoteric, heterocyclic ring with two nitrogen atoms in 1, 3 –position in a five membered ring is called imidazole. Imidazole has a pKa of 14.5, which makes it somewhat more acidic than alcohols but less acidic than phenols, carboxylic acids, and other substances. The conjugate acid has a pKa of roughly 7, which makes it more basic than pyridine as a base **[1]**. The pharmacological actions exhibited by derivatives of imidazoles have attracted the interest of synthetic chemists in the synthesis of new drugs with a range of medicinal applications. It has been observed that compounds of imidazole exhibit anti-tumor, anti-inflammatory, antiviral, anti-ulcer, antibacterial and antifungal properties **[2]**. According to a different study, a compound with the imidazole ring showed the strongest anti-proliferative action against four different cancer cell types, including MCF-7, H1299, HeLa, and B16-F10. Its average IC50 value was 7.219 µM. It is necessary to look into a new justification for anticancer medications in order to find tailored treatments with less systemic adverse effects. Imidazole has the ability to overcome the unresolved drawbacks of clinical medications that are now in the market and might be used as a chemical framework for innovative anticancer treatments that have multiple potential modes of action, according to certain reported studies **[3]**. These five-membered N-heterocycles have several uses due to their straightforward synthesis techniques and ring functionalization. Consequently, efficient and economical methods for selective production have drawn a lot of attention in imidazole chemistry. Therefore, a straightforward and effective method for preparing the imidazole moiety is required **[4]**.

**Classical strategies:**

Imidazole can be synthesized in the laboratory using a variety of techniques, such as Wallach, Debus-Radziszewski, Van Leusen, and others. With these techniques, several substituted imidazoles can be prepared by simply altering the functional groups that are present in the reactants.

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Nidhi Rani etal (2023) **[5]** mentioned that Heinrich Debus created imidazole for the first time in 1858. But as early as the 1840s, other imidazole derivatives were found, which were made by combining formaldehyde and glyoxal [$R_1 = R_2 = H$] with ammonia. Linjie Kong etal (2010) **[6]** prepared 2, 4, 5 – trisubstituted imidazoles by reacting 1, 2 – diketones with an aldehyde in presence of excess ammonium acetate at 180° C for 2 mins in a microreactor under pressure**.**

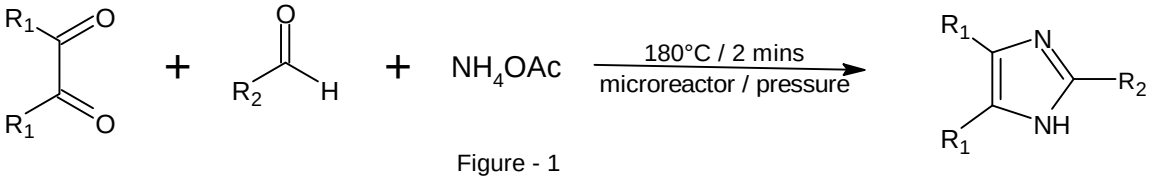



Figure - 1

A. Mazut et al, (2015) **[7]** have shown that interactions between glyoxal and more neutral inorganic ammonium salts such as ammonium sulphate in water at room temperature can generate imidazole, imidazole-2-carboxaldehyde and 2,2-bis-1H-imidazole.

Bao Hu et al. (2011) **[8]** used 2-azido acrylates and nitrones, a highly effective and practical technique for the synthesis of 1,2,4,5-tetrasubstituted imidazoles has been established, this reaction was carried out under moderate conditions.

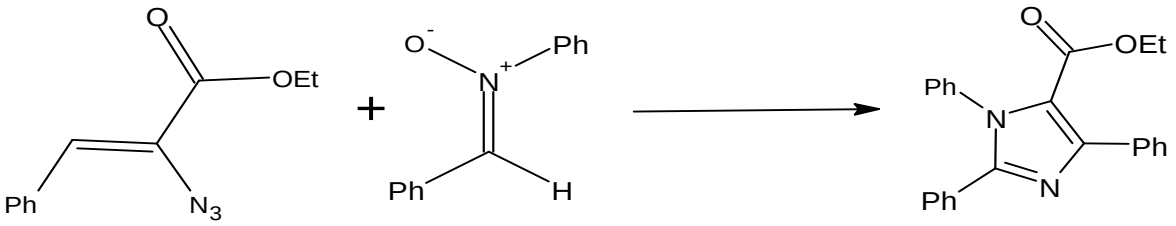



Figure - 2

Ankit Siwach et al. (2012) **[9]** utilized benzil, ammonium acetate, and substituted benzaldehyde, by Radziszewski synthesis techniques to create imidazoles, and the antibacterial characteristics of the resulting compounds were determined.

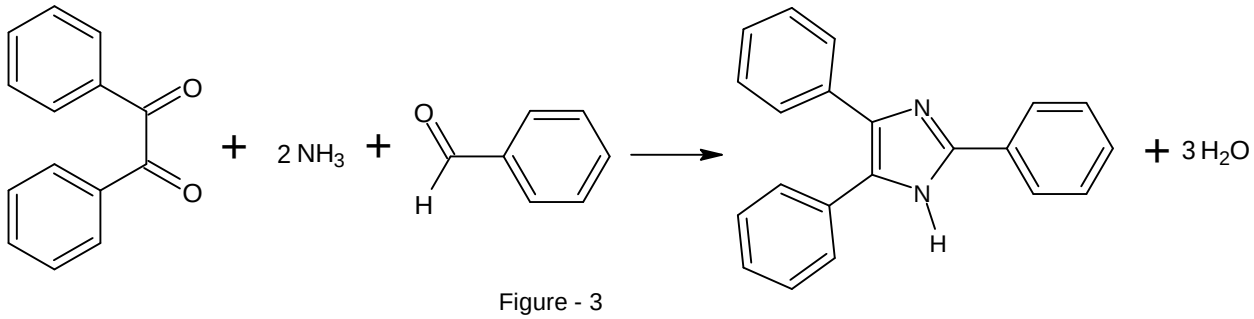



Figure - 3

Ahmad K et al. (2013) **[10]** carried out the above reaction by using ammonium acetate in place of ammonia in presence of potassium permanagnate and copper sulphate as catalyst and refluxing in ethanol. Leyla Poorali et al. (2013) **[11]** also achieved high yields and quick reaction times in the synthesis of tri and tetrasubstituted imidazoles by using benzil, aliphatic or aromatic amines, ammonium acetate, and a catalytic quantity of antimony chloride (or stannous chloride dihydrate) in a solvent-free environment. Using them as efficient and reusable catalysts, new and quick access to the synthesis of unique polysubstituted imidazoles is possible.

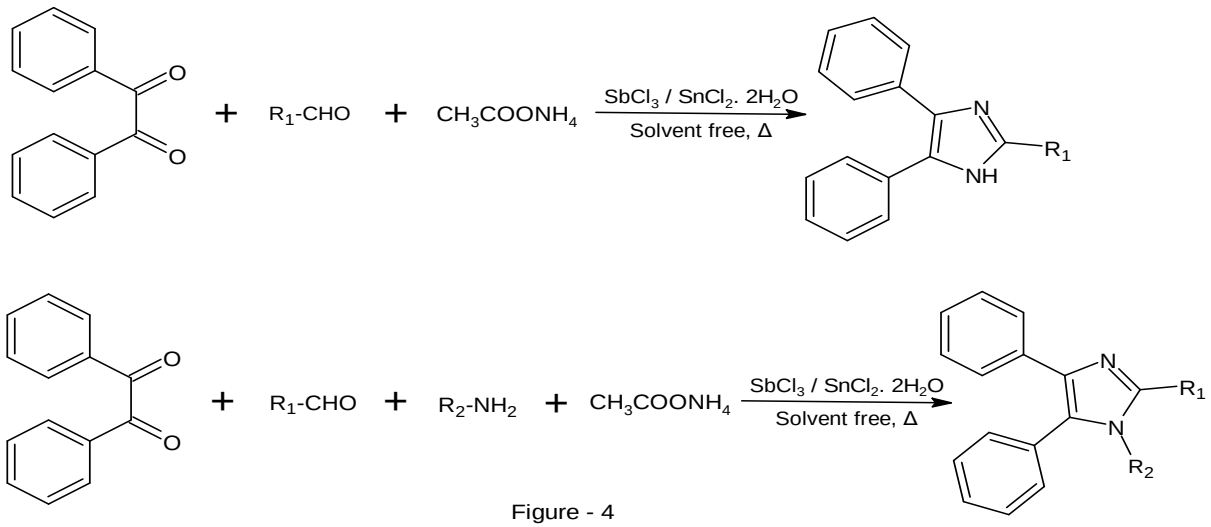



Figure - 4

Ma B.B et al. (2015) **[12]** also carried out Debus-Radziszewski synthesis by the combination of di – tertbutyl tetraone and aromatic aldehyde.

Xunan Zheng et al. (2020) **[13],** Van Leusen et al. (1977) **[14]** mentioned the use of aldimines to prepare substituted imidazoles using the Van Leusen technique by reaction with tosyl methyl isocyanide or even sulfonyl methyl isocyanides respectively.

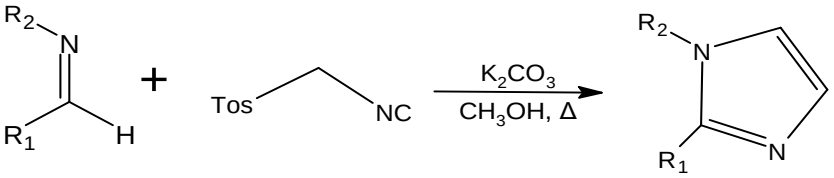



Figure - 5

Benincori, T et al. (1993) [**15]** carried out Wallach synthesis by heating N, N-dimethyl oxamide with phosphorus oxychloride in phosphorus pentachloride giving an intermediate (a), which was then further reduced with HI to generate N-methyl imidazole. This process yields 2-chloro-N-methyl imidazole.

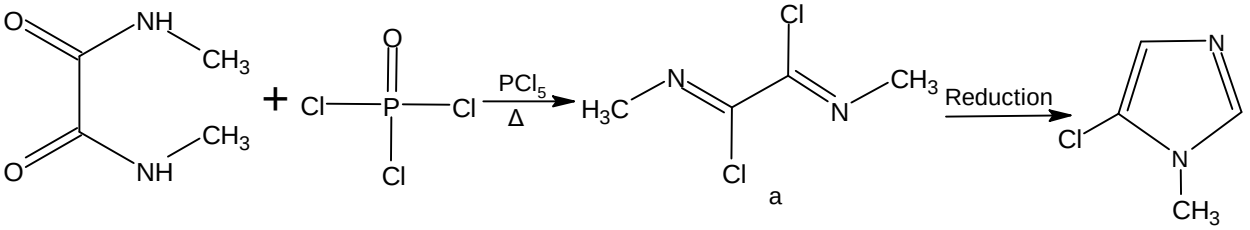



Figure - 6

Ritesh Kumar et al. (2020) **[16]** suggested that in order to prepare imidazole; ethylene diamine and alkyl nitriles can be first reacted in presence of sulphur to produce imidazoline (b), which can then be further dehydrogenated with barium manganate to produce modified imidazole.

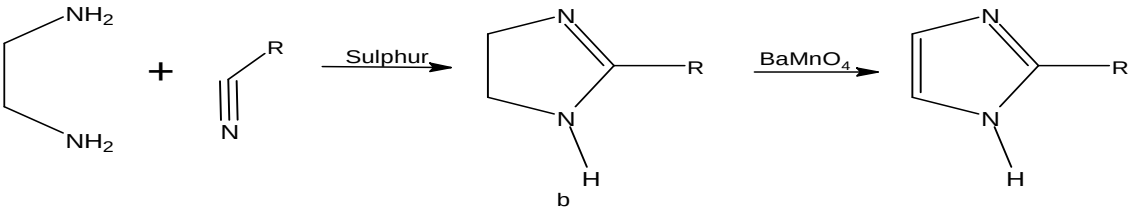
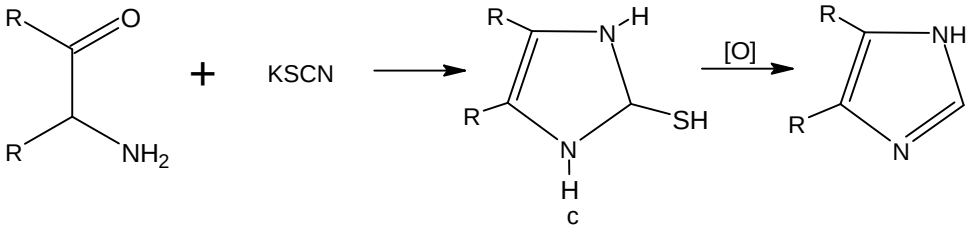



Figure - 7

Deepak Chaudhury et al. (2015) **[17]** included Markwald's imidazole synthesis by using potassium thiocyanide and α-aminoketone to produce an intermediate (c) that could then be further oxidized to produce modified imidazole.




c

Figure - 8

Suma Sanikommu (2020) et al. **[18]** suggested a reaction between the α-halo ketone and amidine to obtain imidazoles. But this method worked well for the synthesis of 2, 4- or 2,5-biphenyl imidazoles.

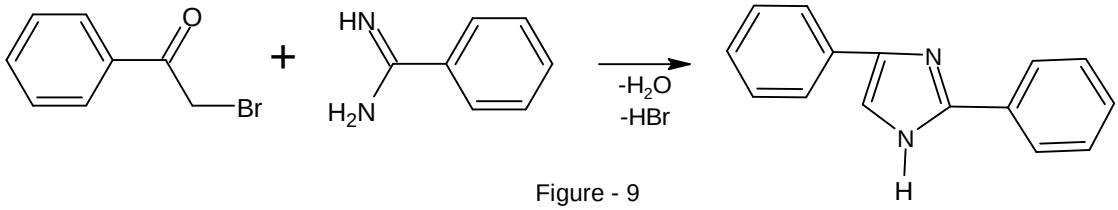
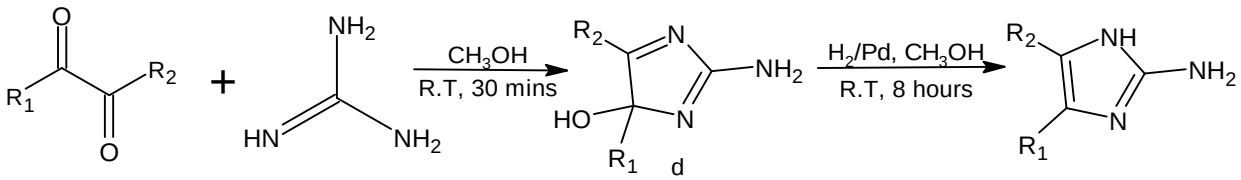



Figure - 9

Nirjhar Saha et al. (2023) **[19]** reported a metal – free synthesis in which alpha diketones reactwith guanidine in the presence of methanol to produce an intermediate (d) which was further reduced with hydrogen gas in presence of palladium catalyst and methanol for eight hours to yield substituted amino imidazole.




d

Figure 10

**A**mmonia can also be used to react with a mixture of tartaric acid dinitrate and modified formaldehyde to form substituted imidazole. In addition, imidazole itself can be produced by heating the dicarboxylic acid produced with quinolone in the presence of copper to yield 2-alkyl imidazole-4, 5-dicarboxylic acid (e), which is then further reacted with aniline to yield 4-substituted benzamide **[20]**.

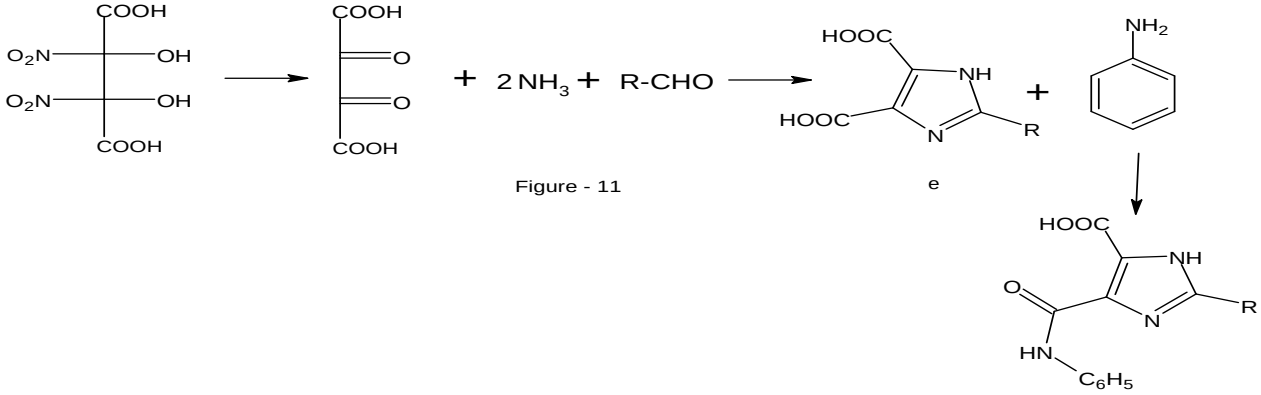
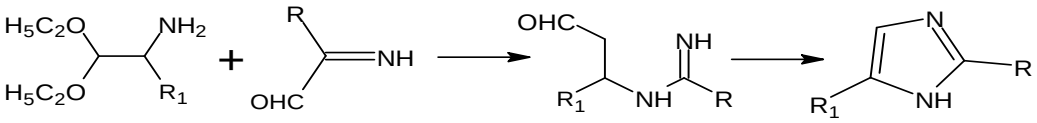



Figure - 11

e

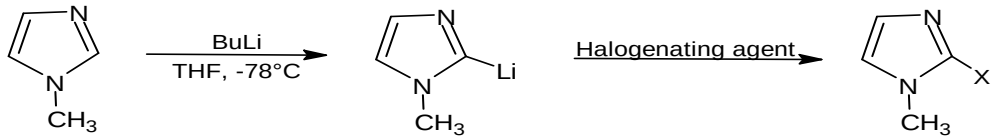
Dipanshu Panday et al. (2020) **[21]** reported that substituted imidazoles can be made by reacting an imidate with a α-aminoacetal or α-aminoaldehyde to generate an imidine (f) that eventually cyclizes by forming a single bond.




f

Figure - 12

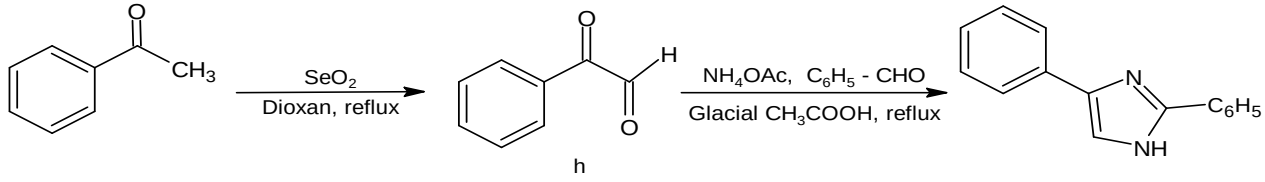
E. V. Aleksandrova et al. (2011) [**22**] suggested lithiating 1-methylimidazole first, then treating the intermediate 2-lithio derivative (g) with a halogenating reagent (e.g. per chloryl fluoride, trichloro acetyl chloride, carbon tetrachloride, hexachloroethane). This is the conventional method for producing 2-halo-1-methylimidazoles (yields 55–80%)**.**




g

Figure - 13

Prashant Tripathi et al. (2023) **[23]** reported a two-step reaction method to generate novel imidazole derivatives. First, aryl ethanones reacted with selenium dioxide in dioxane to give phenyl glyoxal (h), and then aromatic aldehyde was used to cyclize the compound in the presence of acetic acid and ammonium acetate. They also investigated how the produced chemicals affected bacteria.




h

Figure - 14

A. Bhatnagar et al. (2011) **[24**] suggested that benzimidazole is found in Vitamin $B_{12}$ and may be made in a variety of ways that are more significant than imidazole. Specifically, benzimidazole is created when 1, 2-diaminobenzene is heated in an acidic medium and condensed with a carboxylic acid.

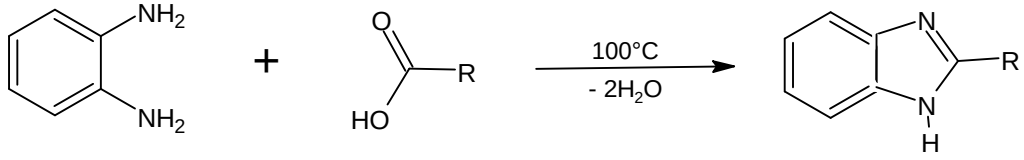



Figure - 15

Ian de Toledo et al. **[25]** reported a method of stepwise oxidation followed by condensation using p-tolualdehyde and acetophenone as exemplar carbonyl substrate. Following considerable optimization, it was found that acetophenone may be catalyzed with 10 mol% aqueous HBr in dimethyl sulphoxide at 85°C to produce equivalent glyoxal (i). After adding a methanol: dimethyl sulphoxide (6:4) solution along with synthesized glyoxal to a mixture of p-tolualdehyde and ammonium acetate in methanol, the necessary imidazole was extracted in a 69% yield**.**

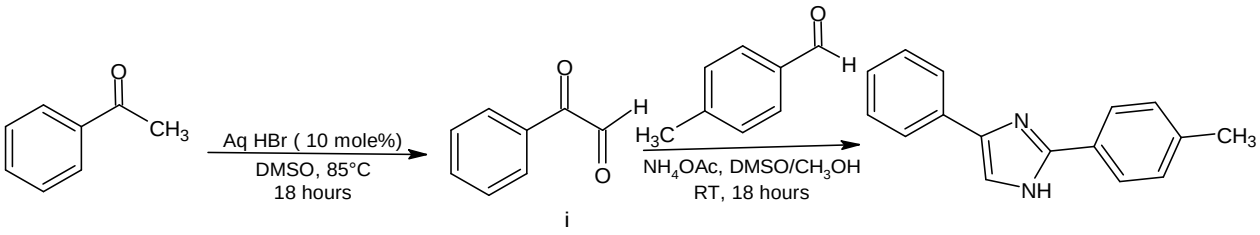



Figure - 16

Louis G et al. (2021) [26**]** carried out efficiency and modularity of metalated isocyanide (j) condensation with nitrogenous π-electrophiles set it apart. An isocyanide can be deprotonated to produce an isocyanide-stabilized anion, which during condensation with a nitrile or imidate yields a transitory imine that easily cyclizes to produce imidazole**.**

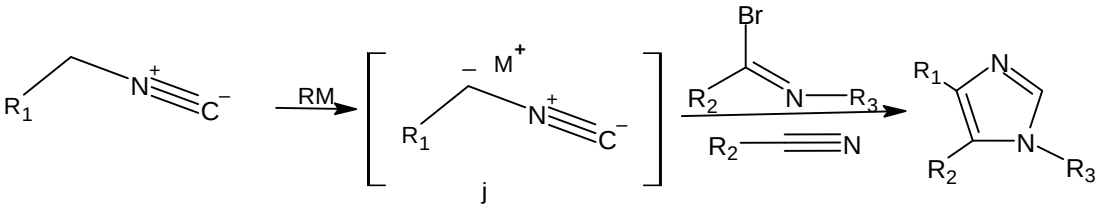



Figure 17

**Green strategies:**

These techniques are essentially a greener way to synthesize the same moieties through the use of environmentally safe processes that have negligible or no impact on the environment. Imidazole synthesis has been carried out by using water, Deep Eutectic Solvent (DES) or Tertiary Butyl Hydro Peroxide (TBHP) as solvents which are environmentally benign **[27]**.

**1) Using Organocatalysts:**

Recently small organic molecules have been used to catalyze organic reactions and this has greatly minimized the use of metal-based catalysts, and the reactions can be carried out even in the presence of water **[28].** Also, carbon dioxide molecules have been used as a one carbon source for synthesis because it is readily available, cheap and non-toxic **[29**].

Doug E. Frantz et al. (2004) **[30]** used thiazolium-catalyzed addition of an aldehyde to an acyl imine producesα-ketoamide in situ, which is then subjected to closing of ring to yield substituted imidazoles in the one-pot synthesis. The Stetter reagent (k), thiazolium salt, acts as anorganocatalyst in this process.

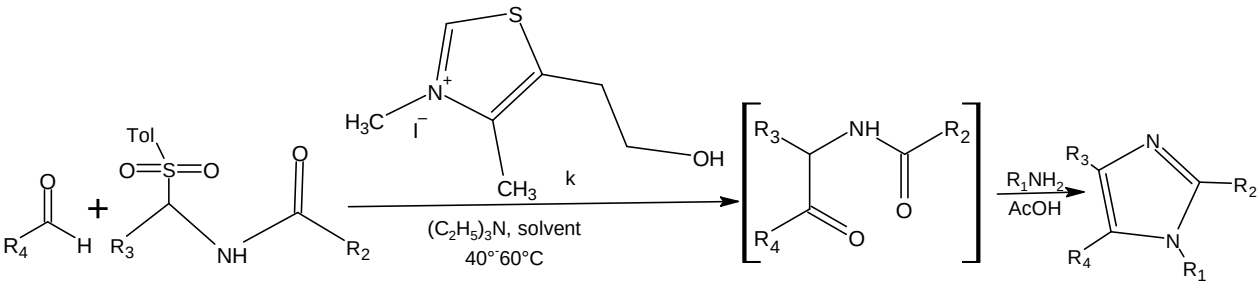



Figure - 18

S. Samai et al. (2009) **[31]** synthesized trisubstituted imidazole derivatives organocatalytically, 1, 2-dicarbonyl compound was reacted with aryl halide, and ammonium acetate at 60°C in presence of 15% L-proline. For tetrasubstituted imidazoles an additional molecule of primary amine was used under similar conditions.

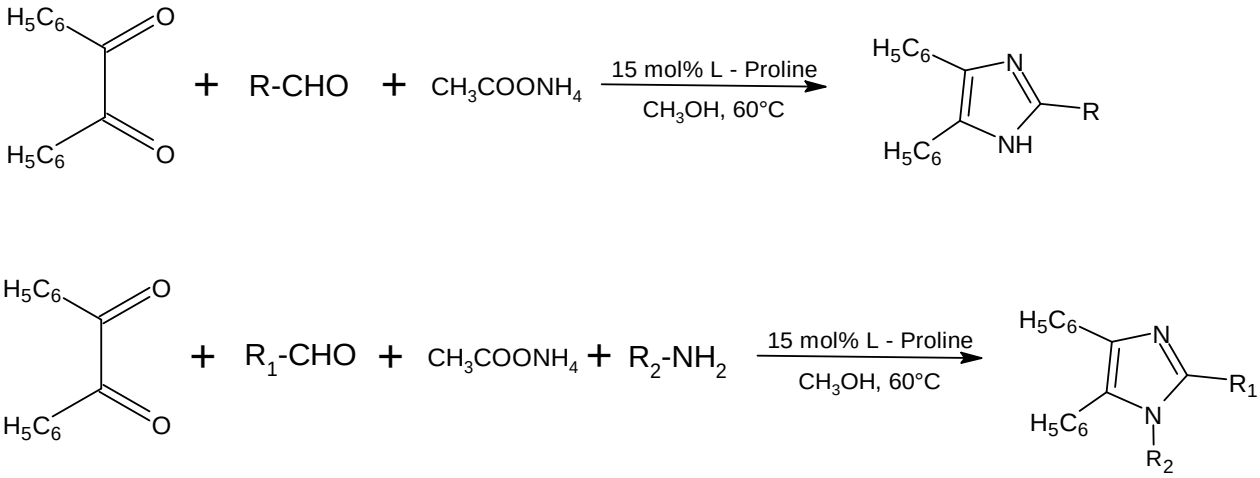



Figure - 19

Jayant Sonar et al. (2019) **[32]** synthesized 2, 4, 5-trisubstituted imidazoles at 160 °C utilizing biodegradable lactic acid, an aromatic aldehyde, benzil, and ammonium acetate. Lactic acid is a green solvent that is safe for the environment and is used in this straightforward process. Additionally, lactic acid is a promoter and is easily produced by the fermentation of carbohydrates.

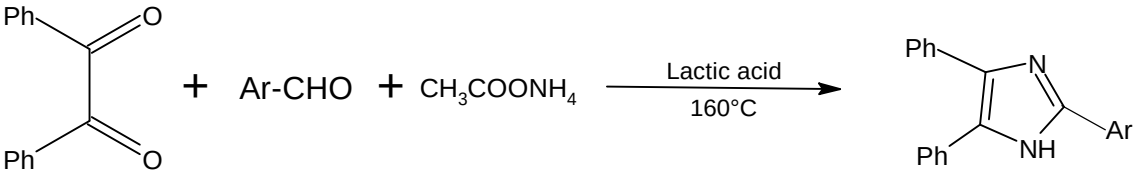



Figure - 20

**2) Using Nanoparticles:**

Mariyam Hajjami et al. (2015) **[33**] developed a second green method in which 2,4,5-trisubstituted imidazole was produced by reacting benzil with a substituted aldehyde in the presence of nano-aluminum nitride catalyst in a solvent-free system at 130°**C** and a few drops of water**.**

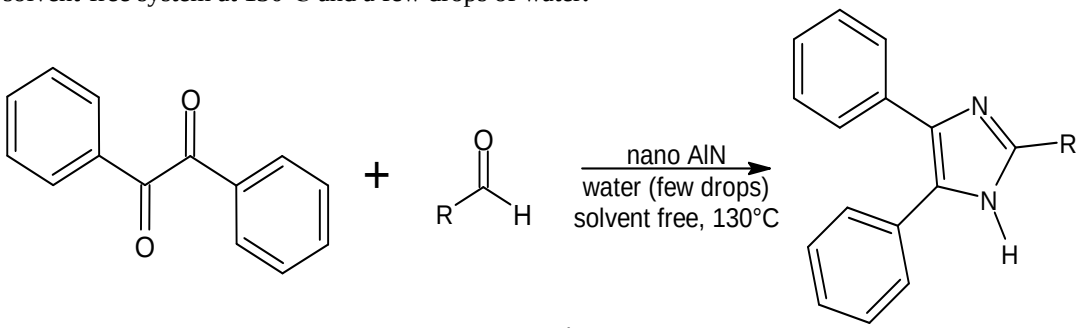



Figure - 21

Sundaram Singh et al. (2019) **[34]** used zirconium oxide nanoparticles in a one-pot multicomponent process involving isatin derivatives, ammonium acetate, and substituted benzaldehydes to create imidazole derivatives.

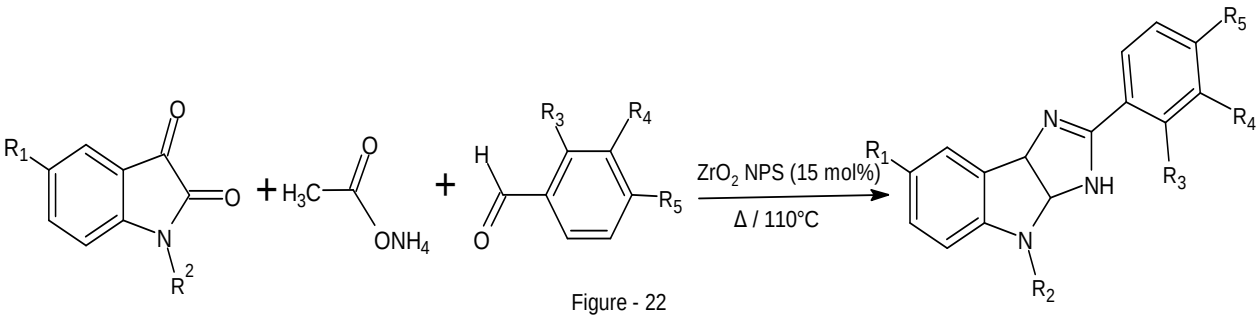



Figure - 22

Myo Thwin et al. (2019) **[35]** used cuaimine and $Fe_3O_4$ (magnetite) magnetic nanoparticles, four component reaction was carried out between benzil, benzaldehyde, aniline, and ammonium acetate under varying time and temperature conditions, solvent types, and solvent-free conditions to create substituted imidazoles.

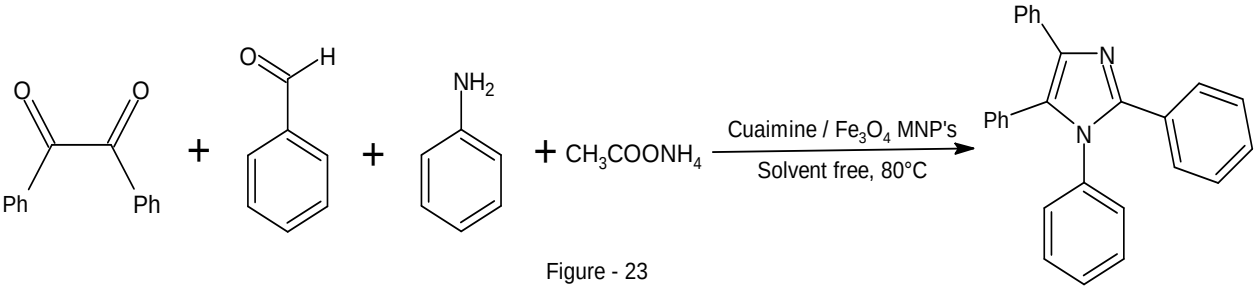



Figure - 23

Liela K. Ahmadi et al. (2022) **[36]** carried out synthesis of $Cr_2O_3$ (chromium oxide) nanoparticles from zingiber extract followed by using as a green catalyst for the microwave-assisted synthesis of imidazole from benzil, aromatic aldehyde, and ammonium acetate.

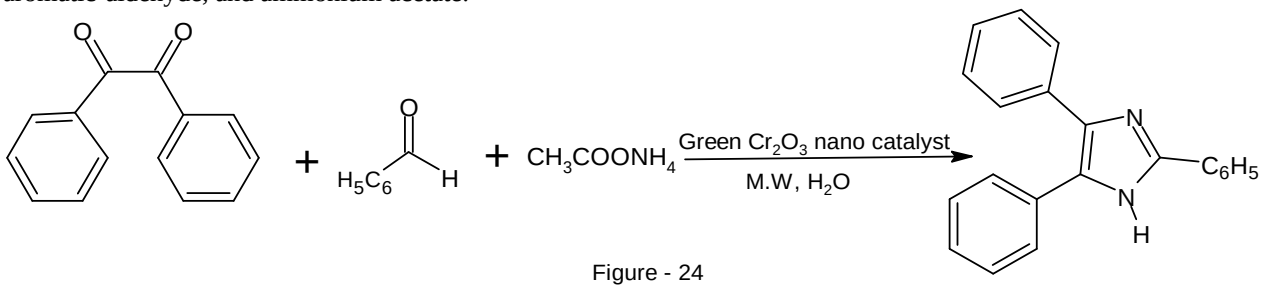



Figure - 24

Also S.M. Bagwan et al. (a) (2022), S.M. Bagwan et al. (b) (2022) [**37, 38]** and Srinivasa Gupta et al. (2019) **[39]** used 15 mol % silver nanoparticles or 15 mol % copper oxide nanoparticles and magnetic nano cobalt ferrite ($CoFe_2O_4$) respectively as catalyst for the same reaction while refluxing in presence of ethanol.

Najmeh Zahedi et al. (2018) **[40]** carried out the above reaction with 9, 10-phenanthraquinone instead of benzil, then the reaction was catalyzed by reusable perovskite-type oxide (nanoparticles) to form phenanthro-imidazole derivative. Esmail Korani (2018) **[41]** and Aravind Gajenji et al. (2022) **[42]** carried out solvent free imidazole synthesis by magnetic core–shell nanoparticles containing $I^{3-}$as a novel catalyst or by ultrasound assisted synthesis using NiO nanoparticles**.**

Heber. V. Tolomeu et al. (2023) **[43]** in a multicomponent synthesis, obtained numerous tetrasubstituted imidazole derivatives using different aldehydes, benzil, ammonium acetate, and prop-2-ynylamine in the presence of nano copper nanoferrite ($CuFe_2O_4$) as a catalyst in 50 % ethanol under reflux for around 50 minutes.

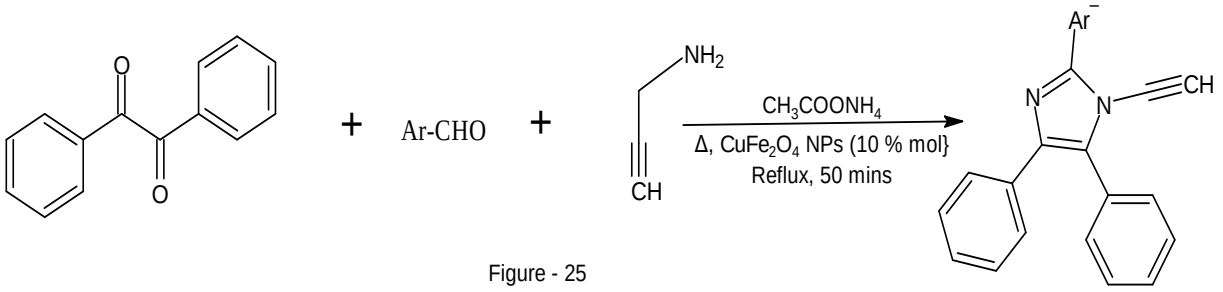



Figure - 25

Nguyen T. Chung et al. (2023) **[44)** reacted o-phenylene diamine with aromatic aldehyde, nanocrystalline magnesium oxide, iodine at normal temperature and acetonitrile as a solvent.

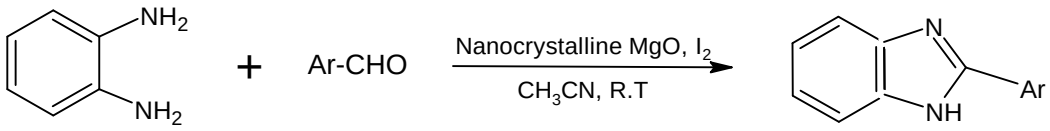



Figure - 26

Najmedin Azizi (2023) **[45]** used simple carbon nitride catalyst encased FeCeOx nanoparticle production for very efficient and reusable substituted imidazole synthesis.

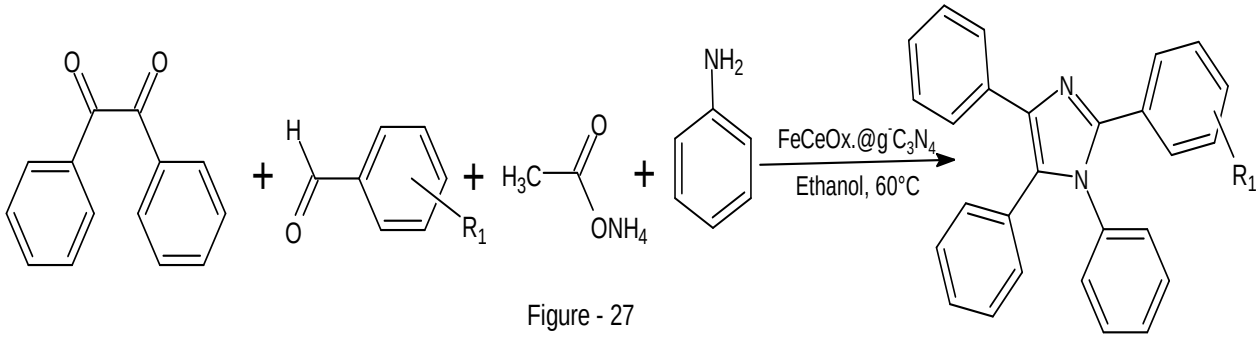



Figure - 27

Hieu etal. (2023) **[46]** reported four-component synthesis of imidazole using benzil/benzoin, aldehydes, primary amines, and ammonium acetate at room temperature and without the use of a solvent, employing 2,6-dimethylpyridinium trinitromethanide {[2,6-DMPyH]C($NO_2$)$_3$} as a catalyst, results in the construction of tetrasubstituted imidazole derivatives.

**3) Using self-catalytic reaction:**

Kiran Pradhan et al. (2016) **[47]** carried out a self-catalytic reaction by solvent-free multi-component synthesis. This was performed by grinding the reactants and then heating them at 150°C and 160°C.

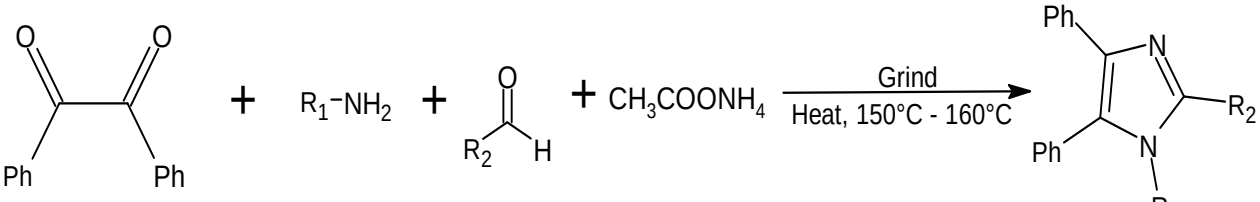



Figure - 28

**4) Using Schiff's base intermediate:**

Pankaj Saxena et al. (2021) **[48]** carried out green imidazole synthesis using Schiff's base intermediate. Sulphanilamide and substituted aryl halide were reacted to produce Schiff's base. Isatin derivative was then acetylated and reacted with Schiff's base in the presence of ammonium acetate using silica gel as solid support to yield imidazole derivative. The synthesized imidazoles exhibited anticancer activity against Hep-2 cell as well as antihelmintic activity.

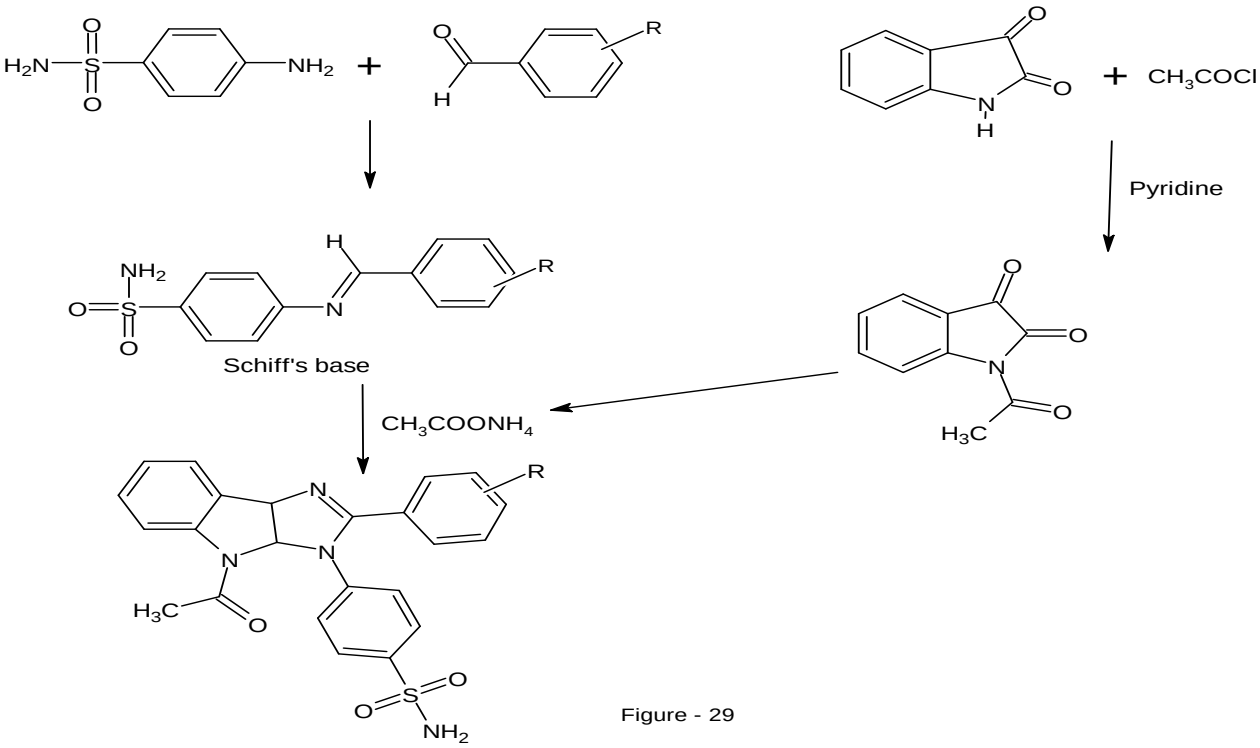



Figure - 29

**5) Using Zeolite catalyst:**

Sudarshan S. Dipake rt al. (2022) **[49]** synthesized 1, 2, 4, 5 - tetrasubstituted imidazole by reacting ammonium acetate, substituted aniline, substituted aryl halide, and benzil in a solvent-free environment. This was done by using a zeolite, ZSM – 11 as a green catalyst.

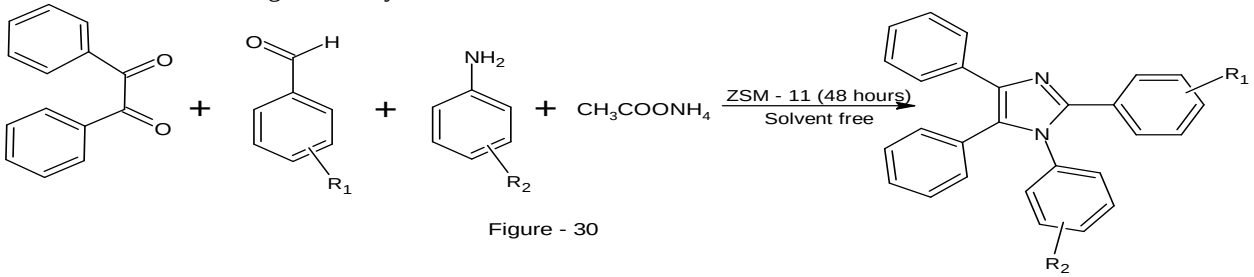



Figure - 30

**6) Using fruit juice catalyst:**

Sushil Gulati et al. (2022) **[50]** used fruit juices as catalysts to synthesize bioactive imidazoles. As a catalyst Citrus limon, Vitis vinifera and Cocos nucifera were added to benzil, aromatic aldehyde and ammonium acetate.

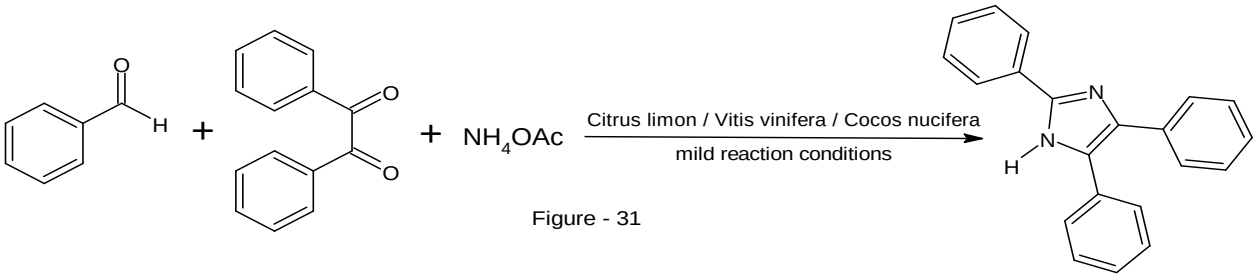



Figure - 31

**7) Using solid acid catalyst:**

Ghodsi M. Ziarani et al. (2015) **[51]** produced 1, 2, 4, 5-tetra-substituted imidazoles by condensing the four components of a 1, 2-diketone - benzil, a substituted aromatic aldehyde, ammonium acetate, and primary amine using sulphonic acid functionalized silica ($SiO_2$-Pr-$SO_3H$) as a highly active heterogeneous solid acid catalyst in solvent-free conditions at a temperature of 140º C.

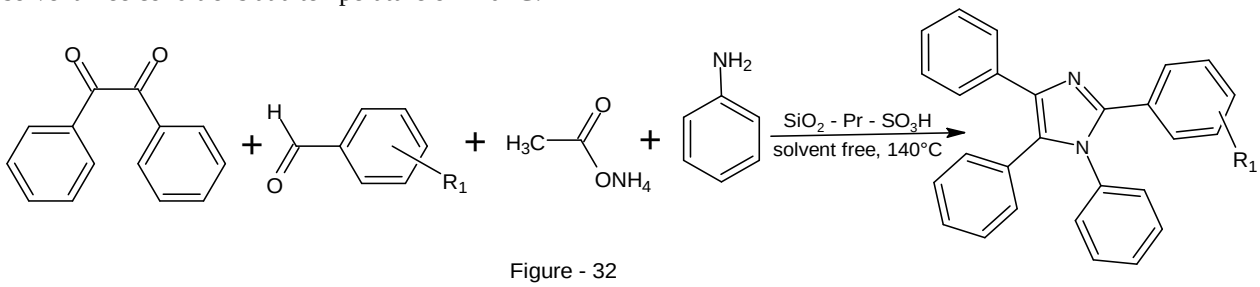



Figure - 32

**8) Using Fly ash:**

P. Ezhilmathi et al. (2019) **[52]** condensed benzil, 2-amino ethyl pyrrolidine, benzaldehyde, and ammonium acetate in ethanol at 80 º C in the presence of fly ash supported $Bi_2O_3$–ZnO catalyst.

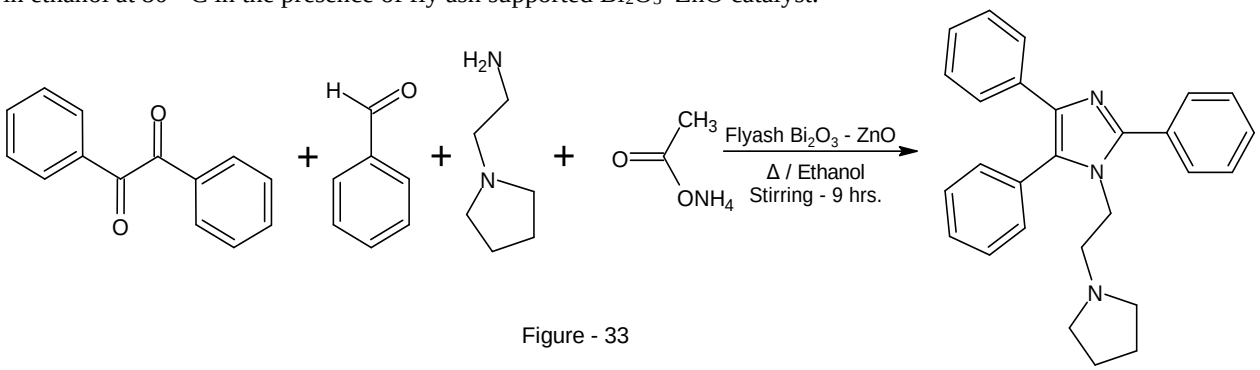
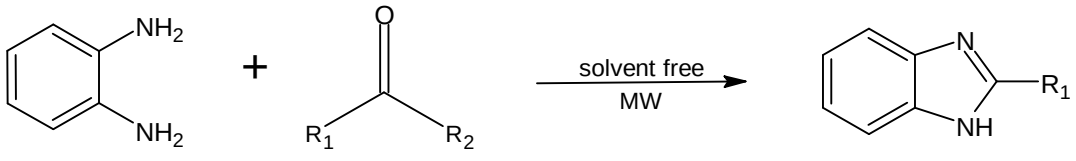



Figure - 33

**9) Using microwaves:**

Modern synthetic organic chemistry got a boost due to the advent of microwave assisted organic synthesis, since the reactions could be carried out in one step using metal free conditions, in short duration of time and with high yields **[53]**.

Na Zhao et al. (2005) **[54]** synthesized benzimidazoles from o - phenylene diamine, carboxylic acid, or acetoacetic ester in solvent free conditions with the aid of microwaves.

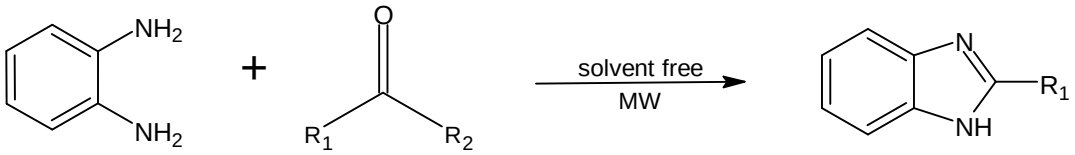



R1- CH3 or C6H5

R2- CH2COOEt or OH

Figure - 34

Javad Safari et al. (2010) **[55]** synthesized 2, 4, 5 trisubsituted imidazole with an effective catalyst like $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ in a single pot and three component condensation of benzil, aryl aldehyde, and ammonium acetate in solvent-free conditions using microwave irradiation.




R1- CH3 or C6H5

R2- CH2COOEt or OH

Figure - 35

Neha Gupta (2017) **[56]** reported that aldehydes, benzil, and ammonium acetate can be microwaved in the presence of ethanol to create 2,4,5-trisubstituted imidazoles in excellent yields**.** This process makes use of a Schiff's base complex nickel catalyst (Ni-C). Haitham D. Hanoon (2019) **[57]** used 8-hydroxy-7-iodoquinoline-5-sulfonic acid (HISA) as a catalyst in this reaction

S.V. Nalageet al. (2010) **[58]** used a green method involving the condensation of benzil, vanillin and ammonium acetate in the presence of polyethylene glycol. Substituted imidazoles were prepared using microwave synthesis. Polyethylene glycol is inexpensive, non-toxic, reusable and easily accessible.

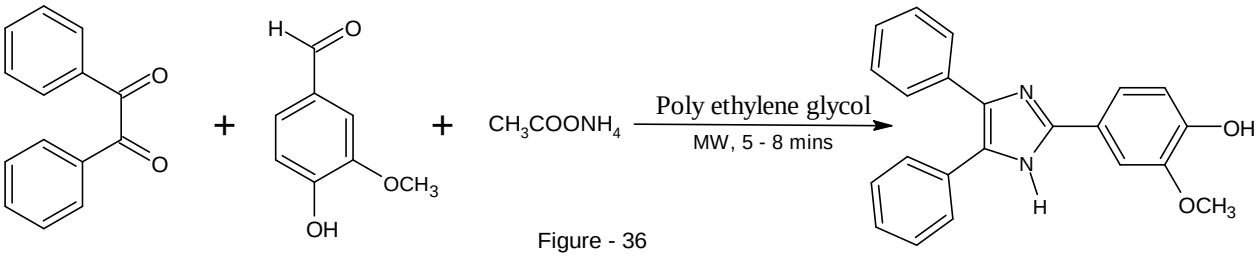



Figure - 36

Arvind B. Tapase et al. (2022) **[59]** obtained 1,2,4,5 – tetrasubstituted imidazole by subjecting benzil, aromatic aldehyde, primary amine, ammonium acetate in presence of sulphamic acid as catalyst. E. Gelens et al. (2006) **[60]** carried out the same reaction with chloroform or acetic acid as solvent under microwaves.

M. Bouchakour et al. (2021) **[61]** synthesized novel disubstituted imidazole by treatment of 1, 2 – dione with ammonium acetate and aldehyde using MW in presence of acetic acid at 180° C for 5 mins.

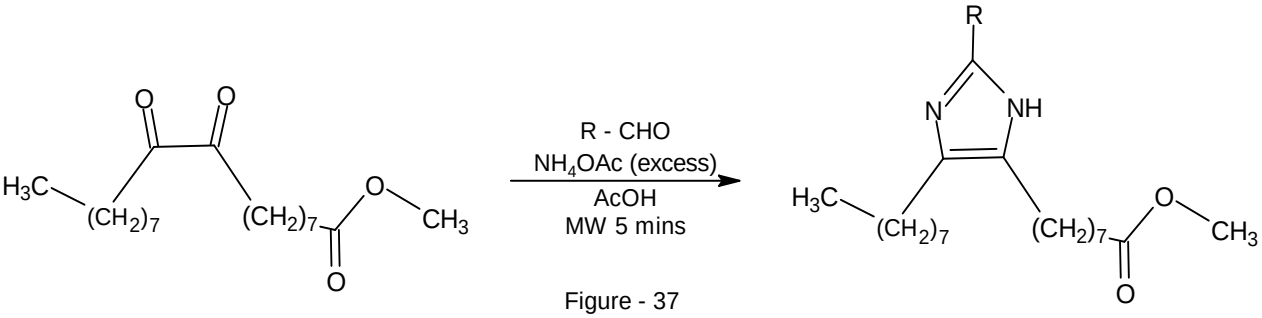



Figure - 37

Pilar M. Fresneda et al. (2001) **[62]** utilized a regioselective synthesis method that combines the cyclization of the resultant ketoamides (l) by ammonium acetate under microwave irradiation after the reaction of azidoacetyl indoles with carboxylic acids in the presence of tertiary phosphines to obtain 2,4-disubstituted imidazoles in two steps.

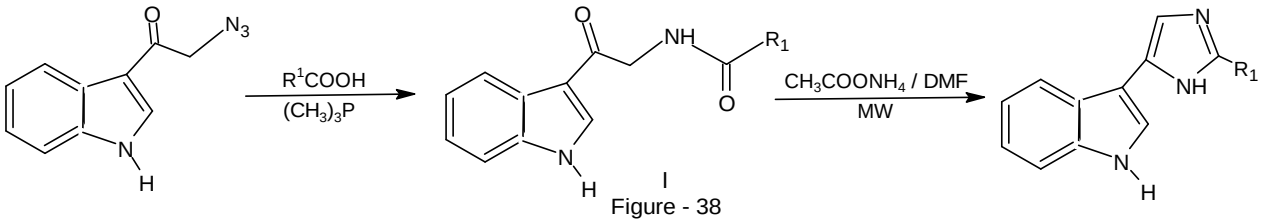



Figure - 38

Poonam Gupta et al. (2015) **[63]** reported that in the presence of acid chloride, 1,2-di(furan2-yl)-2-oxoethyl carboxylates react to generate an intermediate (m) that is then converted to trisubstituted imidazoles by reacting with ammonium acetate under microwave irradiation.

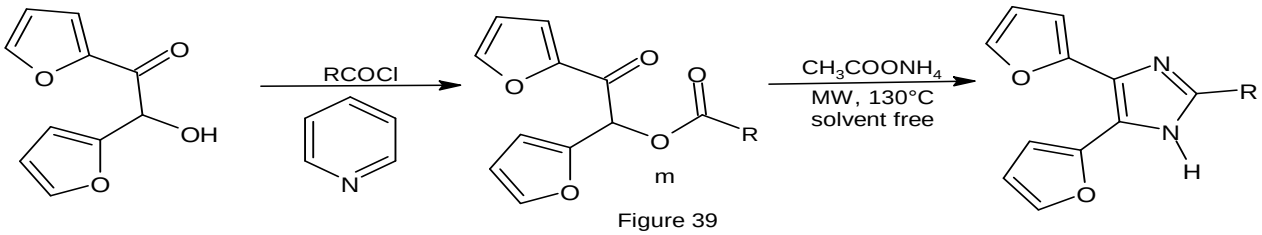



Figure 39

**10) Making use of chalcones - a natural product:**

Chettiyan T F. Salfeena et al. (2018) **[64]** studied the relationship between structure and activity indicating that modified chalcones have improved activity. Additionally, the presence of enone functionality makes it a better precursor for a variety of chemical processes generating imidazoles.

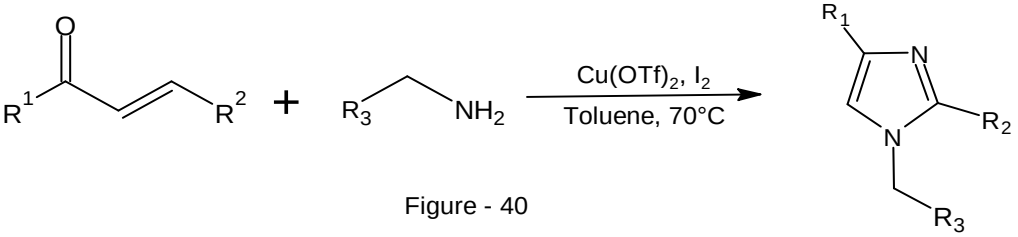



Figure - 40

**11) Catalyst free synthesis:**

N. Naresh Kumar Reddy et al. (2017) **[65]** employed catalyst-free synthesis. Vinyl azides and amidines are oxidatively cyclized by [3+2] cycloaddition with 1, 8-diazabicyclo [5.4.0] undec-7-ene (DBU) under mild conditions, utilizing acetonitrile as a solvent, to produce 2,4-disubstituted imidazoles.

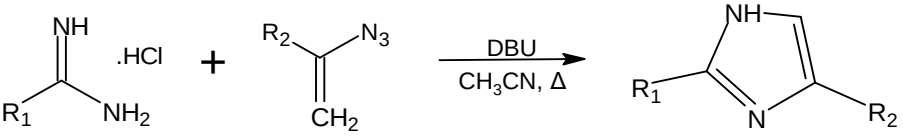



Figure - 41

**12) Without Using Any Solid Surface, Catalyst, or Solvent:**

Swati Samanta et al. (2013) **[66]** made 2,4,5-trisubsituted imidazoles by heating 1, 2-diketone, aromatic aldehyde, and ammonium acetate in a 1:1:3 moleratio for three to six hours at 130°C.

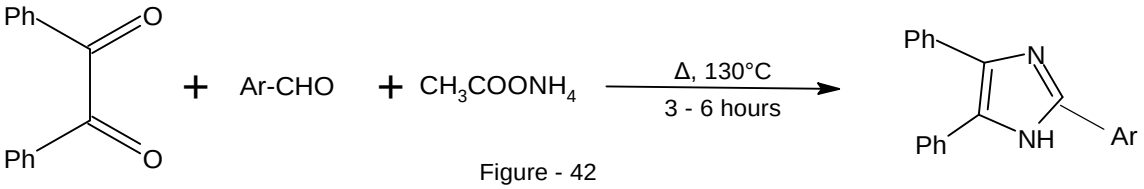



Figure - 42

**13) Using ultrasound:**

Sushant R. Khedkar et al. **[67]** reported a one-pot three-component reaction using an innovative and environmentally friendly $NiFe_2O_4$-geo-polymer nano-catalyst to synthesize imidazole derivatives, with the aid of ultrasonic irradiation. The nano-$NiFe_2O_4$ supported on geo-polymer proved to be an excellent recyclable catalyst.

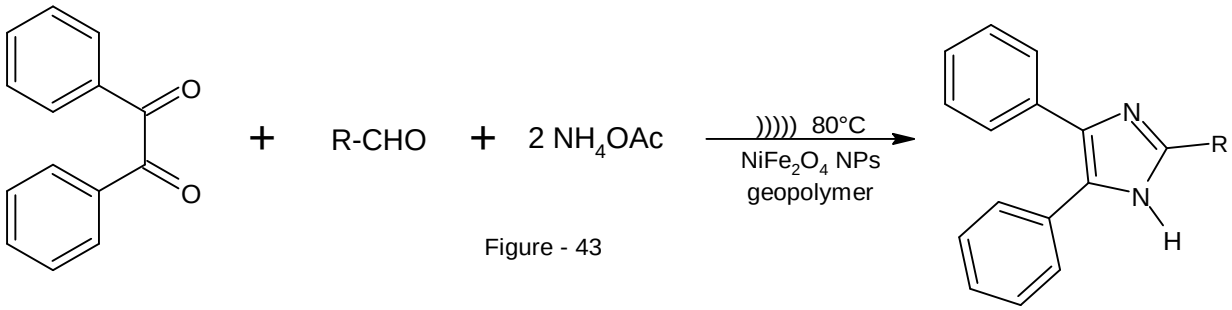



Figure - 43

Xian-Long Yu etal. (2023) **[68]** reported thatthis reaction was also carried out by ultrasound-assisted protocol giving high yields of imidazoles, up to 97% by using $Fe_3O_4$ magnetic nano particles (MNPs) as catalyst. Faezeh Shafaeiaetal (2019) **[69]** reported that these magnetic nanoparticles are reusable provided they are used in solvent free conditions at 50°C

Debasree Saha et al. (2024) **[70]** reported the synthesis of corresponding imidazole derivatives by ultrasonic irradiation of 1,2-diketones (benzil/anisil) and aromatic aldehyde in the presence of ammonium acetate and the HMS-SA (Hexagonal Mesoporous Silica – Solid Acid) catalyst.

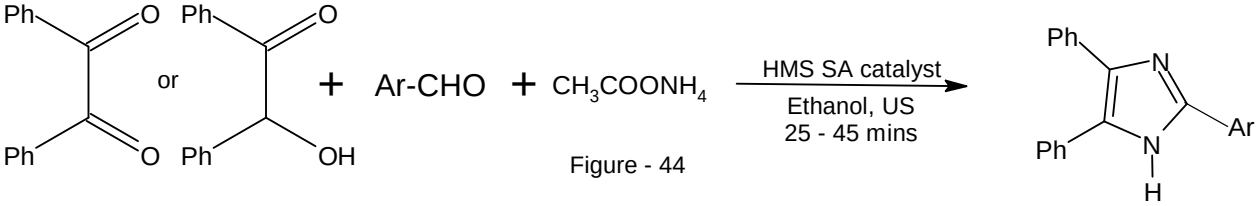



Figure - 44

Alicia R. Arellano etal. (2016) **[71]** reported that aromatic aldehydes and ethylene diamine were reacted with ultra-sound using NBS as an oxidant and water as a solvent, yielding good to outstanding results in 12–18 minutes. After being assessed as Mono Amine Oxidase (MAO) inhibitors, the resultant imidazolines showed good selectivity and activity in the micro molar (μM) range.

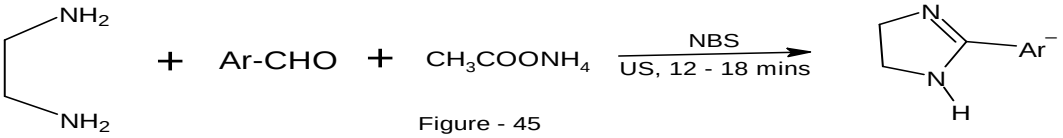



Figure - 45

D. S. Zinad et al. (2020) **[72]** showed that the stability and formation rate of synthesized compounds can be further investigated by theoretical calculations, such as DFT and thermodynamic studies.

**Conclusions: -**

We have covered the most up-to-date, easy, and eco-friendly techniques for making imidazoles. When synthesizing imidazoles, research chemists might choose from a variety of conventional or environmentally benign methods. Thus, chemists could attempt to prepare molecules based on the above methods by changing some of the pharmacophores to obtain compounds having profound therapeutic effects and minimum toxicity.

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