Review Article

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Current progress in the synthesis of imidazoles and their derivatives via the use of green tools

https://doi.org/10.1515/hc-2022-0175
received November 27, 2023; accepted March 24, 2024

Abstract: Imidazoles have a unique position in heterocyclic chemistry as these constitute the basic framework of several bio-molecules. Thus, increasing research is being carried out on the synthesis of imidazoles and their derivatives, mainly because of the application of imidazoles in pharmaceutical and medicinal research. Keeping sustainability in mind, researchers are developing synthetic pathways for the synthesis of imidazoles and their derivatives by employing techniques involving green tools, thus leading to sustainable pathways. In this review, we aim to compile such synthetic methodologies involving green tools for the synthesis of imidazoles. The review will cover the synthetic reactions that involve green tools such as microwave irradiation, ultrasound irradiation, and ball milling. We aim to highlight the scope and relevance of such green tools in today's synthetic research. Through this review, we wish to contribute towards the synthesis of imidazoles that serve as a useful class of heterocyclic compounds involved in the development of pharmaceutically active molecules. We sincerely hope that this review will serve as a relevant guide for future sustainable research in the synthesis of imidazoles and their derivatives.

Keywords: heterocycles, imidazoles, microwave, ultrasound, ball milling

1 Introduction

Imidazoles are an integral part of heterocyclic chemistry and form the core structure of many biologically active compounds like histidine, biotin, and histamine [1]. Imidazoles exhibit a range of biological activities such as anti-allergic, anti-inflammatory, antitumor, antiprotozoal, antiparasitic, antibacterial, anti-ulcerative, and antidiabetic [2–10]. Imidazoles are thus starting materials for a range of biologically and industrially applicable molecules.

Several conventional methods of imidazole synthesis have been reported in the literature [11–16]. A few groups have implemented an inherent greener strategy for the synthesis of nitrogen-based heterocycles [17–30]. In the last few decades, green chemistry has become a popular choice in organic synthesis as environmental sustainability is the necessity of the day. Thus, synthetic chemists all around the globe are trying to develop alternative sustainable pathways to conventional modes. This has paved the way for better and more in-depth research on imidazole synthesis via green tools like microwave heating, ultrasound irradiation, ball milling, use of nonhazardous solvent, and/or ionic liquids as reaction medium to name a few. These tools usually involve high yields, low waste, short reaction times, low energy requirement, and often minimize the use of organic solvents in synthesis, thus making the protocols greener in nature.

As a part of our contribution towards the development of greener methods of heterocycle synthesis, in this review, we show the impact of these green tools for the sustainable synthesis of imidazoles and their derivatives. We produce a compilation that includes most of the recent examples of imidazole synthesis via the use of these green tools. The review comprises three subsections, namely, the synthesis of imidazoles via microwave irradiation, the synthesis of imidazoles via ultrasound irradiation, and the synthesis of imidazoles via ball milling. We create a platform that can be used as a standard piece of reference by future scientists working on sustainable methods of heterocycle synthesis.

2 Synthesis of imidazoles via microwave irradiation

Microwave irradiation is a green alternative to conventional (thermal) heating and not only accelerates the

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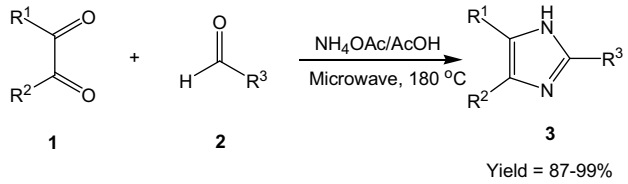


R^1 = C_6H_5, 3-furyl, 4-MeO_2C-C_6H_4, 4-Me-C_6H_4, 2-Me-C_6H_4, 3-MeO-C_6H_4, 4-MeO-C_6H_4, ^{n}Pr

R^2 = C_6H_5, 3-furyl, 4-MeO_2C-C_6H_4, 4-Me-C_6H_4, 2-Me-C_6H_4, 3-MeO-C_6H_4, 4-MeO-C_6H_4, Me

R^3= C_6H_5, 4-F-C_6H_4, 4-CN-C_6H_4,4-MeO-C_6H_4, 3-tetrahydrofuryl, 3-(2-pyridin-4yl-1H)-indolyl

Scheme 1: Synthesis of imidazoles from 1,2-diketones and aldehydes under microwave irradiation.

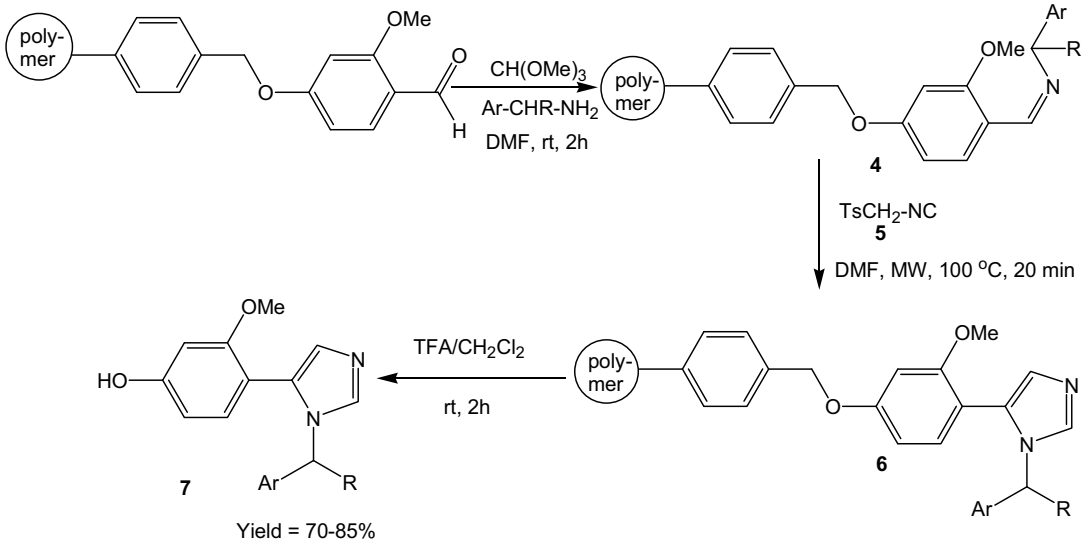
reaction, leading to high yields in short reaction times but also improves the product selectivity. Microwave heating results in mass production at a low cost and is energy-saving; it also provides a sustainable pathway. Since the last couple of decades, microwave irradiation has been used as an efficient tool for the synthesis of imidazoles [31].

In 2004, Wolkenberg and his co-workers reported the synthesis of 2,4,5-trisubstituted imidazoles **(3)** via the reaction between 1, 2-diketones **(1)** and aldehydes **(2)** in the presence of ammonium acetate under microwave irradiation (Scheme 1) [32]. The reactions were fast and quite high-yielding, leading to the formation of a library of substituted imidazoles.

Several diversely substituted 1,2-diketones were compatible with the methodology. Aldehydes with both electron-donating and electron-withdrawing groups participated quite well in the reaction. To demonstrate the versatility and applicability of the protocol, the authors extended the methodology to synthesize Lepidiline B and Trifenagrel, both of which are biologically active imidazole-based molecules.

Kauhaluoma and his group developed a microwave-assisted methodology of disubstituted imidazole synthesis via 1,3 dipolar cycloaddition reaction between *p*-toluenesulfonylmethyl isocyanide **(5),** and imines immobilized on polymer support **(4)** (Scheme 2) [33]. The pure product **(7)** was separated from the resin support by treatment with trifluoroacetic acid. The main advantage of the method is the formation of imidazole products with high yields and purity. One shortcoming of the protocol is the presence of resin appendage (4-hydroxy-2-methoxyphenyl) as a fixed 5-substituent in the imidazole product **(7)**.

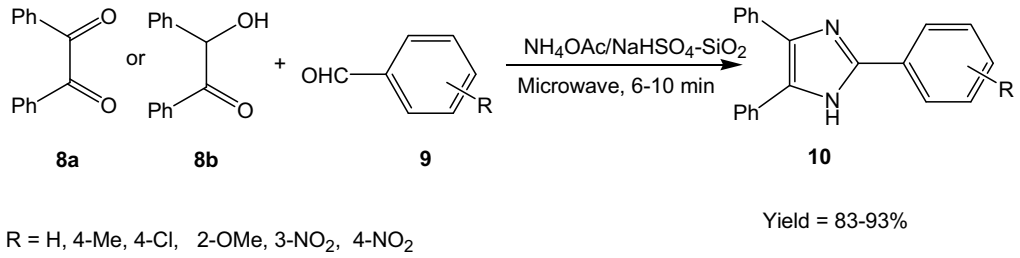
Heravi et al. synthesized trisubstituted imidazole derivatives **(10)** through a solvent-free microwave-assisted protocol involving the reaction between 1,2 diketones **(8a)** or 2-hydroxyketones **(8b)**, aldehydes **(9)**, and ammonium acetate supported on $NaHSO_4$–silica (Scheme 3) [34]. The use of



Ar =C_6H_5, 1-naphthyl, 4-MeO-C_6H_4, 3,4-Cl_2-C_6H_4, 2-MeO-C_6H_4, 3-Cl-C_6H_4, 4-F-C_6H_4,

R = H, Me

Scheme 2: Microwave-assisted synthesis of imidazoles from *p*-toluenesulfonylmethyl isocyanide and imines immobilized on polymer support.

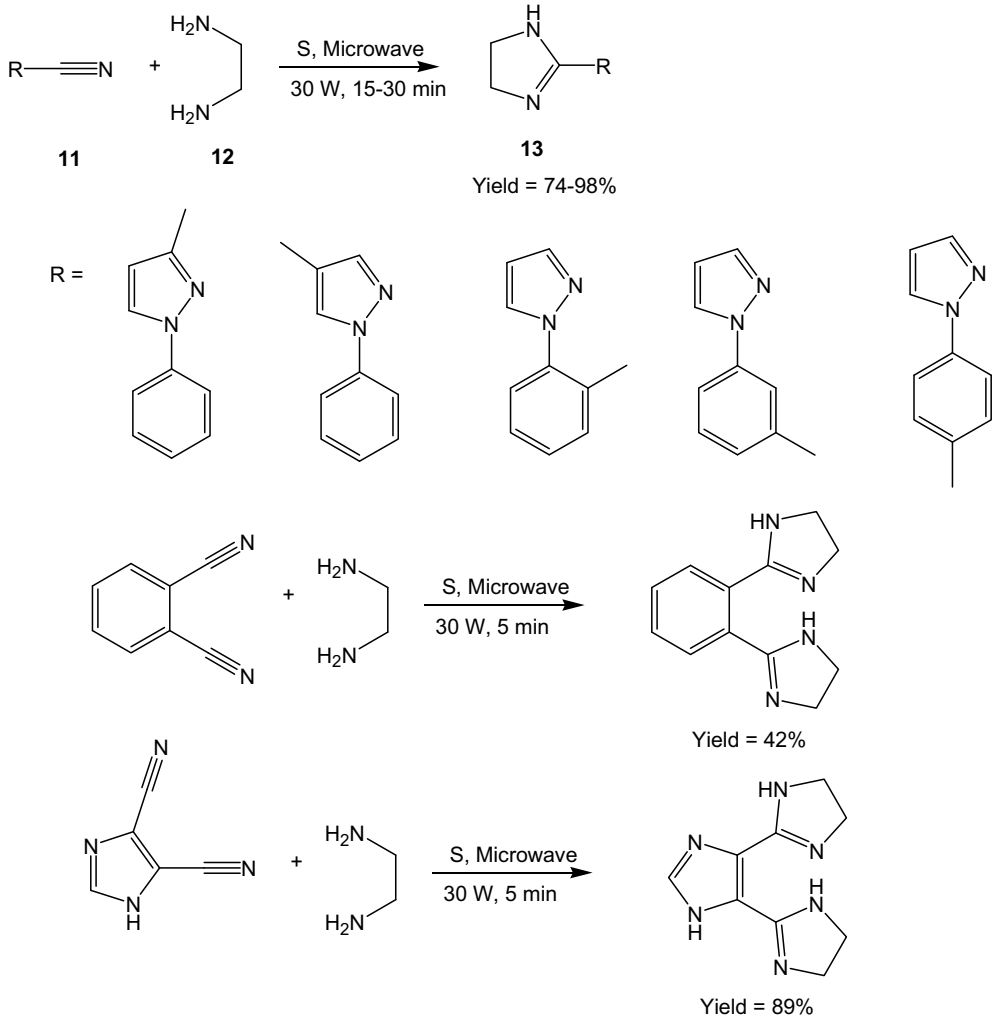


Scheme 3: Solid-phase synthesis of imidazoles under microwave irradiation.

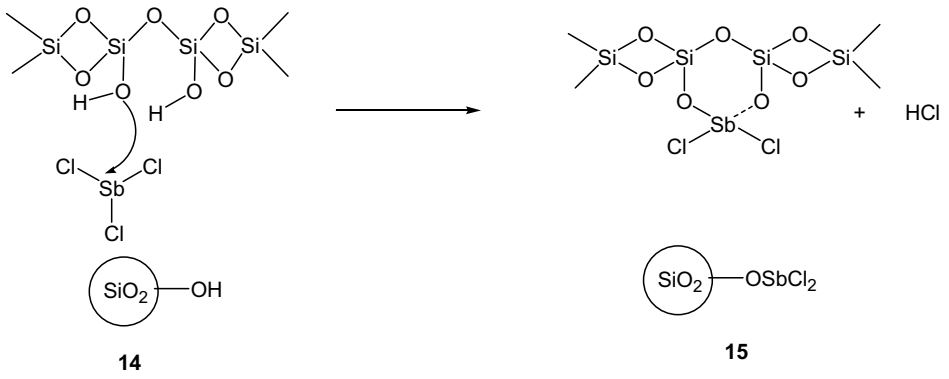
either silica or $NaHSO_4$ as a solid support resulted in lower yields than silica and $NaHSO_4$ combined.

The reaction avoids the use of any solvent and even proceeds with a non-aqueous workup, making it truly a green methodology. The method offers an eco-friendly and economical approach to the synthesis of imidazoles in short reaction times with high yields.

A solvent-free microwave-assisted synthesis of imidazolines and imidazoles was reported by Hoz and his coworkers in 2006 [35]. The method involves the synthesis of 2-substituted imidazolines (**13**) via cyclization of nitriles (**11**) with ethylene diamines (**12**) in the presence of sulphur (Scheme 4). Imidazolines were oxidized to the corresponding imidazoles by oxidation with Magtrieve™ (a chromium



Scheme 4: Microwave-assisted synthesis of imidazolines.



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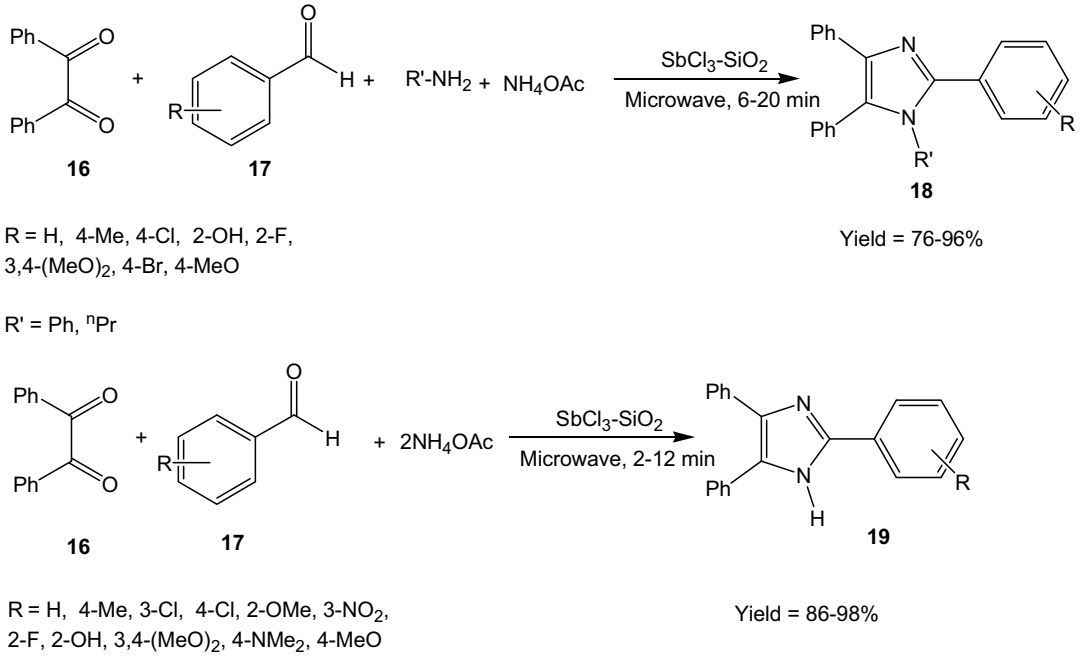
Scheme 5: Formation of the $SbCl_3$–SiO_2 catalyst.

dioxide-based oxidant) under microwave irradiation. The authors chose Magtrieve™, as it is an environmentally benign oxidant and can be separated magnetically and reused. Five of the imidazoline and imidazole products were characterized by X-ray crystallography, which showed that the molecules contained helical chains of N–H···N hydrogen bonds.

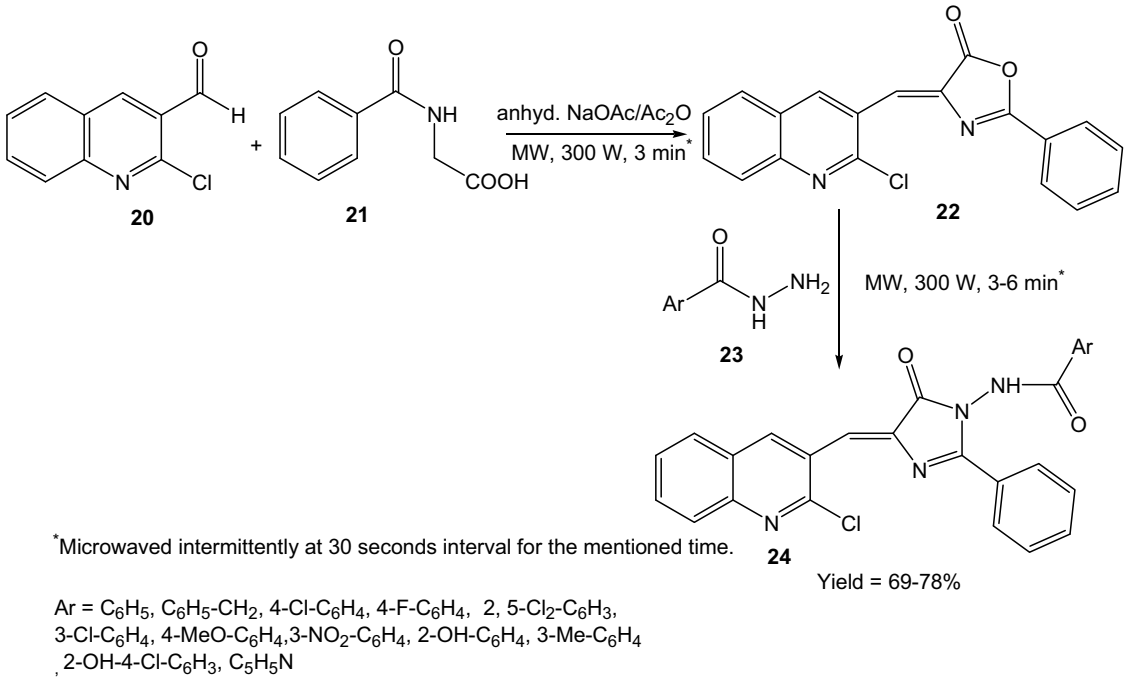
Safari and his group prepared an antimony chloride catalyst supported on silica based on a previously reported literature method (Scheme 5) [36] and used this catalyst for the synthesis of substituted imidazole derivatives under microwave irradiation without the use of any organic solvent (Scheme 6) [37]. The method involved the reaction between 1,2-diketones **(16)**, aldehydes **(17)**, ammonium acetate, and/or amines in the presence of $SbCl_3/SiO_2$ as a catalyst leading to the formation of substituted imidazoles **(18/19)**. The authors also carried out the reaction under conventional heating, and it was observed that under microwave irradiation, the yields were much better in shorter reaction times than in conventional heating.

$SbCl_3$ is quite toxic, and thus the immobilization of $SbCl_3$ on the silica support resulted in a relatively safer use of the chemical. Post reaction, the supported $SbCl_3$ catalyst could be easily separated by filtration and reused for successive runs without appreciable loss of activity. The methodology is thus environmentally and economically sustainable.

Desai and his group developed a green microwave-assisted alternative for the synthesis of quinoline-based



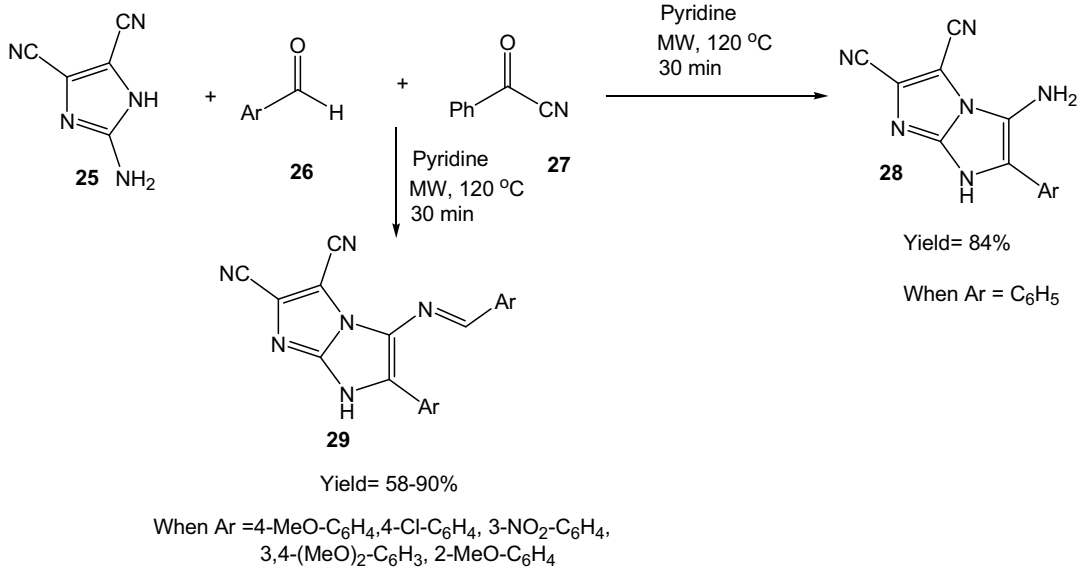
Scheme 6: $SbCl_3$–SiO_2 catalysed synthesis of imidazoles under microwave irradiation.



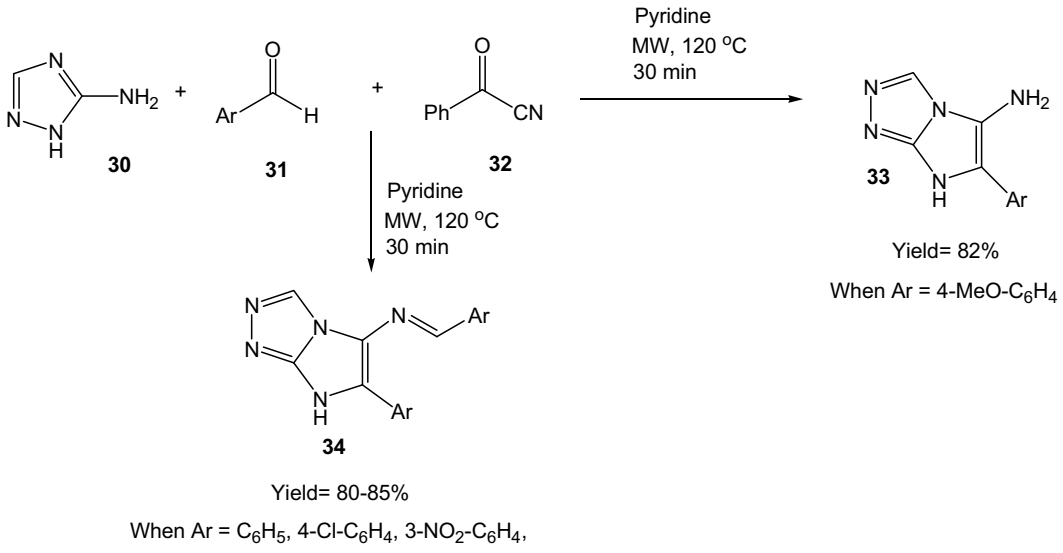
Scheme 7: Synthesis of quinoline-based imidazoles under microwave irradiation.

imidazoles that are biologically important [38]. The method involves the Perkin condensation reaction between 2-chloroquinoline-3-carbaldehyde **(20)**, hippuric acid **(21)**, and acetic anhydride in the presence of sodium acetate under microwave irradiation. The resultant 4-((2-chloroquinolin-3-yl)methylene)-2-phenyloxazol-5(4*H*)-one **(22)** is then treated with N-aminoarylcarboxamides **(23)** under microwave irradiation to produce the desired quinoline-based imidazoles **(24)** (Scheme 7) in significantly high yields within a few minutes.

The authors compared conventional methods of heating to microwave irradiation, wherein microwave irradiation was found to be much better in terms of yield, reaction times, in addition to environmental sustainability. Five of these imidazoles showed high antimicrobial activity.



Scheme 8: Synthesis of imidazo[1,2-*a*]imidazole derivatives under microwave irradiation.

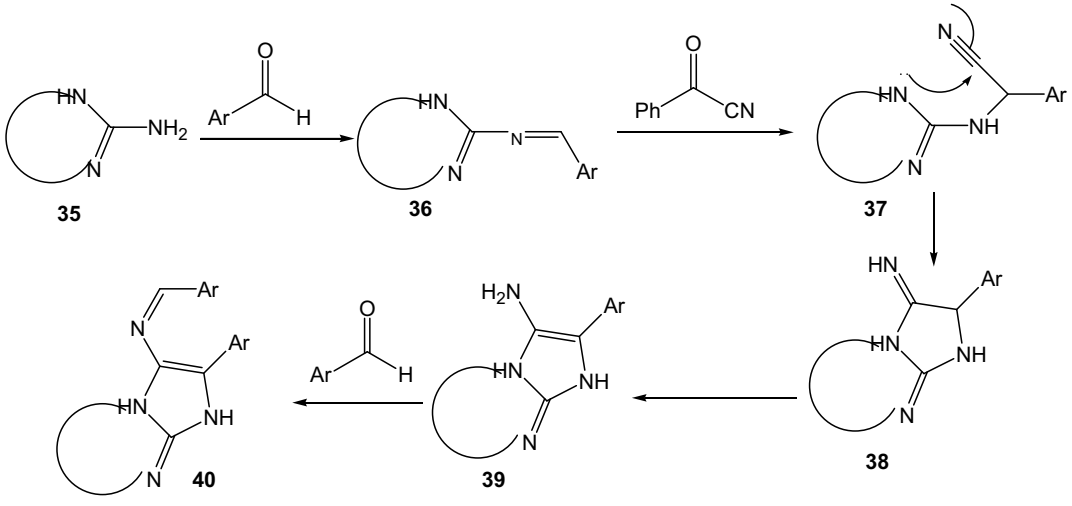


Scheme 9: Synthesis of imidazo[2,1-*c*][1,2,4]triazole derivatives under microwave irradiation.

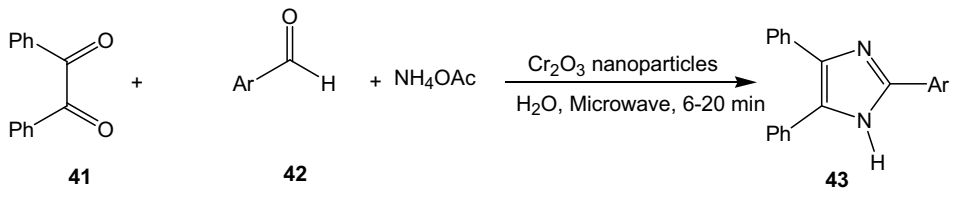
Abdel-Hameed and his co-workers reported an operationally simple, environmentally friendly method for the synthesis of imidazole derivatives via the Strecker reaction between benzoyl cyanide **(27/32)**, aromatic aldehydes **(26/31)**, and 2-aminoimidazole-4,5-dicarbonitrile **(25)**/3-amino-1,2,4-triazole **(30)** under microwave irradiation [39]. When 2-aminoimidazole-4,5-dicarbonitrile is used, 1*H*-imidazo[1,2-*a*]imidazole derivatives **(28/29)** are formed (Scheme 8) while the use of 3-amino-1,2,4-triazole resulted in imidazo[2,1-*c*][1,2,4]triazole derivatives **(33/34)** (Scheme 9). The authors also proposed a mechanism for the reaction that proceeds via the formation of a Schiffs base (Scheme 10).

In most of the previously reported methods of imidazole derivative synthesis via the Strecker reaction, a toxic cyanide source like trimethylsilyl cyanide, cyanamide, or cyanohydrin is used. Abdel-Hameed and his group eliminated the use of toxic cyanide sources, thus making the protocol environmentally benign. In addition, microwave heating led to increased reaction rates in short reaction times with high yields and low waste generation. The process is thus a sustainable alternative for the synthesis of triazole-based imidazole derivatives via the Strecker reaction.

Very recently, in 2022, Marjani and his group developed a green method of preparation of Cr_2O_3 nanoparticles from



Scheme 10: Plausible mechanism for the synthesis of imidazo[1,2-*a*]imidazole derivatives and imidazo[2,1-*c*][1,2,4]triazole derivatives under microwave irradiation.



Ar = C_6H_5, 4-Br-C-C_6H_4, 4-F-C_6H_4, 2-Cl-C_6H_4, 4-Cl-C_6H_4, 4-MeO-C_6H_4,3-NO_2-C_6H_4, 4-OH-C_6H_4, 4-Me-C_6H_4, 2-OMe-C_6H_4

Scheme 11: Cr_2O_3 nanoparticles catalysed the synthesis of imidazoles from 1,2-diketones and aldehydes under microwave irradiation.

Zingiber officinal (Ginger) extract. The resultant Cr_2O_3 nanocatalyst was characterized by scanning electron microscopy (SEM), TEM, XRD, FT-IR, and VSM techniques.

The authors employed this Cr_2O_3 nanocatalyst for the synthesis of imidazole derivatives **(43)** via the reaction between aldehydes **(42)**, benzil **(41)**, and ammonium acetate under microwave irradiation with water as solvent (Scheme 11) [40]. The reaction proceeds in a few minutes, giving high yields of products. Differently substituted aryl aldehydes were compatible with the methodology. However, the presence of electron-withdrawing groups like nitro in the aryl aldehyde part required more time to produce the corresponding product. The nanocatalyst could be recycled for six successive runs without significant loss of activity.

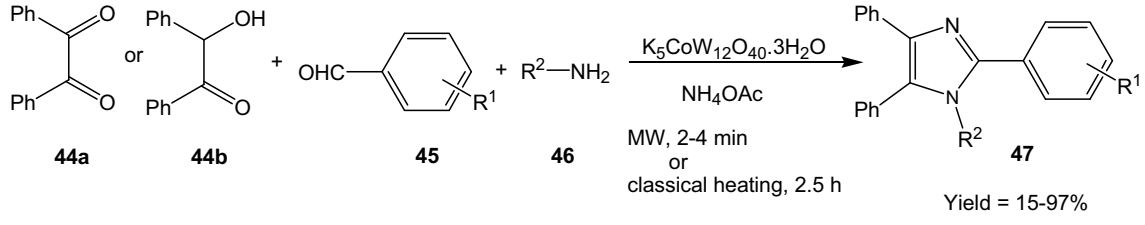
Nagarapu and his co-workers developed an efficient protocol for the synthesis of tetrasubstituted imidazoles via the reaction of benzil/benzoin **(44)**, benzaldehyde **(45)**, amine **(46)**, and ammonium acetate in the presence of potassium dodecatungstocobaltate trihydrate ($K_5CoW_{12}O_{40}{\cdot}3H_2O$) as a catalyst (Scheme 12) [41]. The methodology could proceed both under microwave irradiation and classical heating. The reaction resulted in the formation of tetrasubstituted imidazoles in high yields under solvent-free conditions.

The catalyst could be recovered and reused for six successive runs without appreciable loss in catalytic activity.

3 Synthesis of imidazoles via ultrasound irradiation

Ultrasound irradiation is a convenient method for carrying out reactions that are difficult to proceed under thermal heating. The main advantages of ultrasound irradiation are a great reduction in reaction time, operational simplicity, and increased purity of products with fewer by-products, thus minimizing waste, making workup procedures easy, and conserving energy. Ultrasound irradiation is thus a suitable alternative to conventional heating and serves as a sustainable tool in the synthesis of organic molecules [42–44].

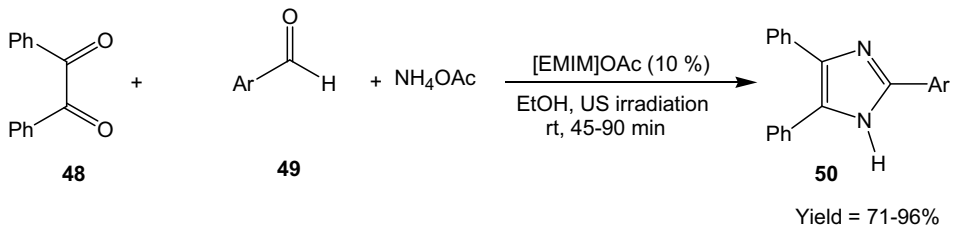
In 2010, Cheng and his group employed an ionic liquid, 1-ethyl-3-methylimidazole acetate, as a catalyst for the one-pot synthesis of 2-aryl-4,5-diphenyl imidazoles **(50)** from the three-component reaction between benzyl **(48)**, aromatic aldehydes **(49)**, and ammonium acetate under ultrasonic irradiation at room temperature (Scheme 13) [45].



R^1 = H, 4-Me, 4-Cl, 3-Cl, 2-OH, 3-OH, 4-OH, 4-NO_2, 3-OH, 3-F, 4-Br, 4-NMe_2, 3,4-$(OMe)_2$, 4,5-OCH_2O-3-OMe

R^2= 4-F-Ph, 4-Cl-Ph, -CH_2Ph, 4-Me-Ph, R(+)phenethyl, cyclohexyl

Scheme 12: Potassium dodecatungstocobaltate trihydrate-catalysed synthesis of imidazoles under microwave irradiation.



Scheme 13: Ionic liquid-catalysed synthesis of imidazoles from 1,2-diketones and aldehydes under ultrasonic irradiation.

The ionic liquid, 1-ethyl-3-methylimidazole acetate [EMIM]OAc, was found to be crucial for the reaction to proceed. The effect of ultrasonic irradiation was also studied by comparing the reaction yields with and without ultrasonic irradiation. The reaction yields without ultrasound irradiation (with high-speed stirring) were extremely low, which showed that ultrasound irradiation was indispensable for the reaction. The authors attributed this to the phenomenon of cavitation that is generated by ultrasound, which led to the enhancement of the reaction. The protocol is an important development in sustainable synthesis as it proceeded at room temperature under mild conditions, followed by an easy workup procedure.

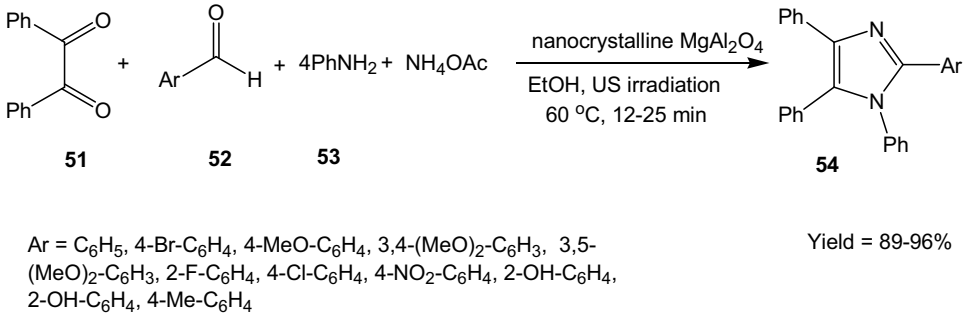
Safari et al. synthesized nanocrystalline magnesium aluminate spinel ($MgAl_2O_4$) and used it as a catalyst for the synthesis of tetrasubstituted imidazole derivatives **(54)** via multicomponent coupling of 1, 2-diketone **(51)**, aldehyde **(52)**, amine **(53)**, and ammonium acetate under ultrasound irradiation. A variety of aldehydes containing either electron-donating or electron-withdrawing functionalities participated in the reaction quite well, leading to high yields of the product imidazole (Scheme 14) [46].

The authors proposed a plausible mechanism that involves the formation of a diamine intermediate followed by a nucleophilic attack of the diamine to the carbonyl of benzil. Finally, cyclization and dehydration led to the product imidazole.

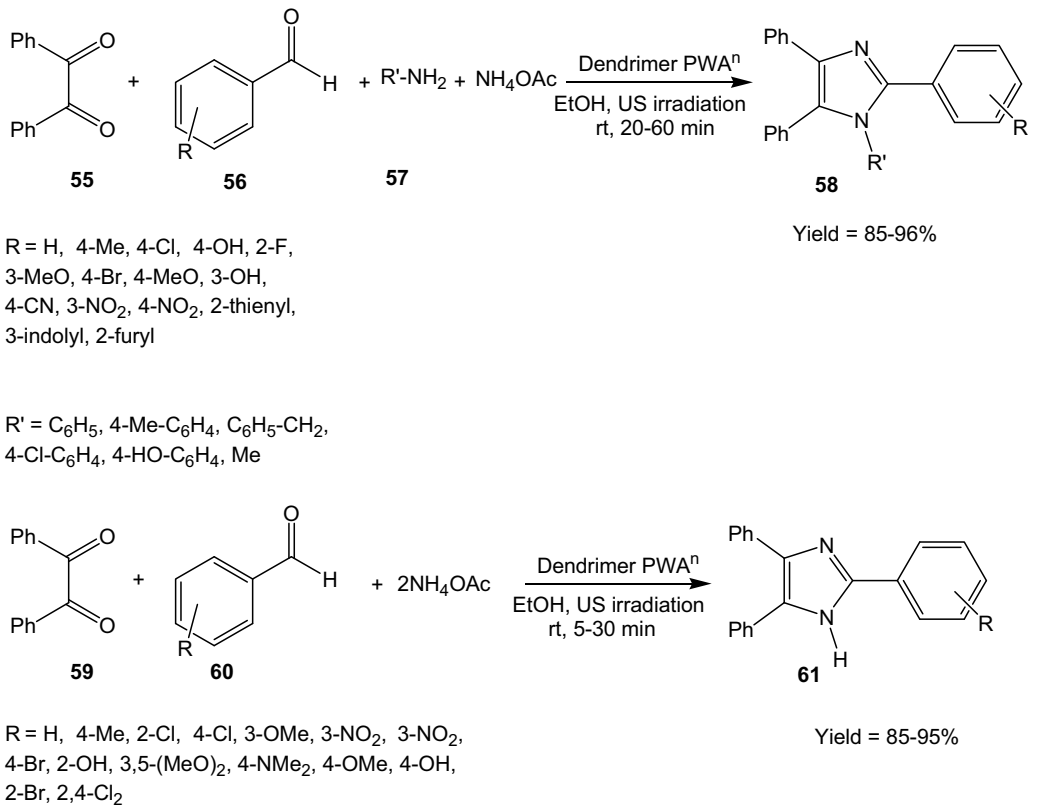
In 2016, Esmaeilpour and co-workers developed dendrimer-encapsulated phosphotungstic acid nanoparticles supported on nanosilica (Dendrimer-PWA^n) [47]. This nanocatalyst was characterized by X-ray diffraction, thermogravimetric analysis, TEM, SEM, DLS, FT-IR, N2 adsorption–desorption isotherm analysis, UV-vis, and elemental analysis.

In the following year, this catalyst was employed by the same group for the synthesis of imidazole derivatives **(58/61)** through a one-pot condensation reaction under ultrasonic irradiation (Scheme 15) [48]. The authors compared the reaction under ultrasonic irradiation with the reaction under conventional heating in solvent-free conditions and it was observed that the reaction under ultrasound irradiation gave comparable yields in shorter reaction times. A wide range of aromatic aldehydes participated in the reaction leading to high yields of the product imidazole. However, aldehydes containing electron-withdrawing groups required shorter reaction times than aldehydes with electron-donating groups. The Dendrimer PWA^n catalyst could be recycled at least six times without appreciable loss in catalytic activity. Effective reusability of the catalyst made the protocol economically sustainable.

Sharma and his co-workers synthesized hollow magnetic spheres functionalized with sulphamic acid groups (HMS-SA catalyst) and employed this as an efficient catalyst for the synthesis of pharmaceutically important imidazole



Scheme 14: $MgAl_2O_4$-catalysed synthesis of imidazoles from 1,2-diketones and aldehydes under ultrasonic irradiation.



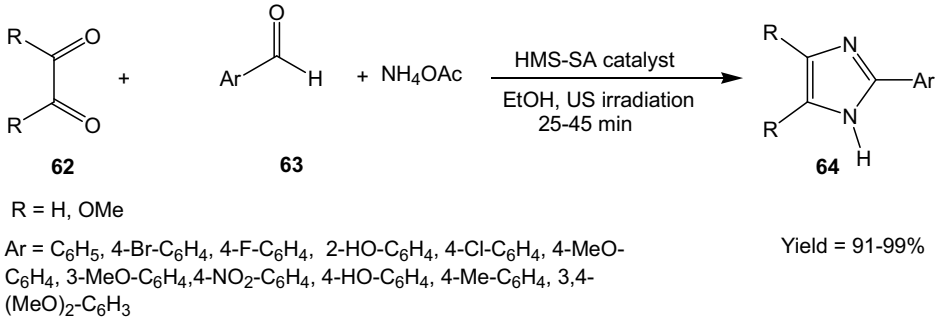
Scheme 15: Dendrimer PWA^n-catalysed synthesis of imidazoles under ultrasonic irradiation.

derivatives (Scheme 16) [49]. Benzaldehydes **(63)** were made to react with 1,2-diketones (benzil/anisil) **(62)** in the presence of ammonium acetate and the HMS-SA catalyst under ultrasonic irradiation to yield the corresponding imidazole derivatives **(64).**

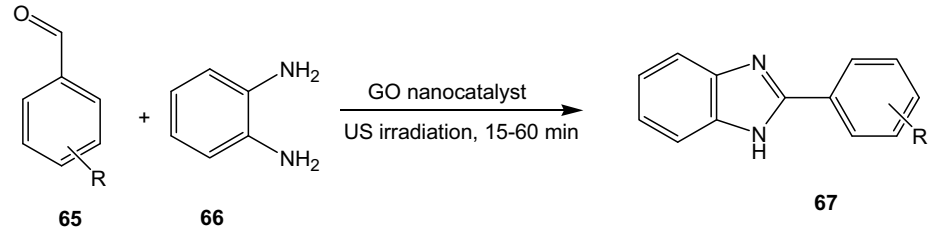
The reaction methodology is characterized by short reaction times, clean reactions, high selectivity, low waste generation, and conservation of energy via ultrasonic irradiation. The catalyst could be recovered magnetically and reused for nine runs with negligible loss in activity, thus adding to the sustainable features of the protocol.

In 2020, Manafi and his group developed a graphene oxide-based nanocatalyst, which was characterized by FT-IR, transmission electron microscopy, SEM, and atomic force microscopy. The catalyst was used for the synthesis of benzimidazoles **(67)** from aldehydes **(65)** and 1,2-benzenediamine **(66)** under ultrasonic irradiation under solvent-free conditions (Scheme 17) [50]. The reaction proceeded under thermal conditions as well.

The methodology has several advantages: short reaction times, high yields, reusability of the catalyst, and most importantly, solvent-free protocol that resulted in a reduction of environmental waste.



Scheme 16: HMS-SA-catalysed synthesis of imidazoles from 1,2-diketones and aldehydes under ultrasonic irradiation.



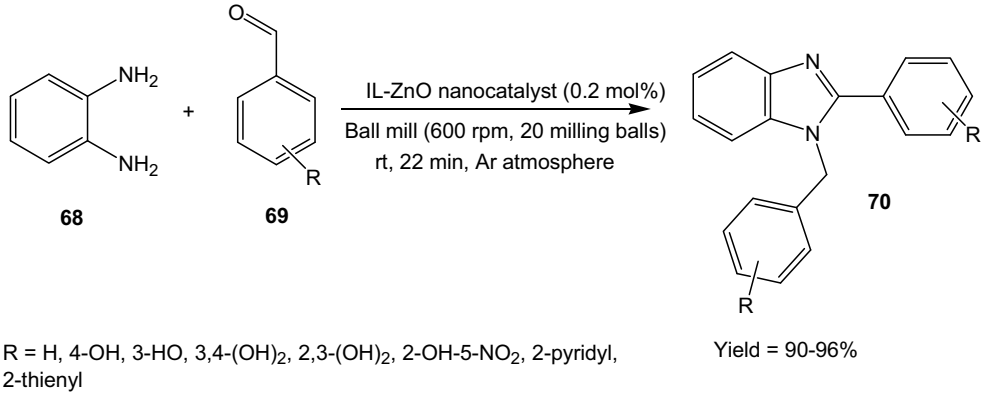
Scheme 17: Graphene oxide nanocatalyst-catalysed synthesis of benzimidazoles aldehydes and 1,2-benzenediamine under ultrasonic irradiation.

4 Synthesis of imidazoles via ball milling

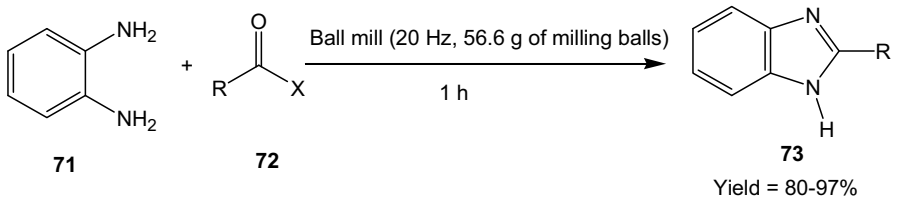
Solvent-free synthetic organic reactions are viewed as environmentally benign pathways as these avoid the use of toxic organic solvents and are highly relevant in academia and industries in order to maintain sustainability. Ball milling serves as the most important tool among solvent-free reaction strategies. In the ball-milling method, the substrates and reagents are put inside a container containing grinding balls, which are shaken at a very high speed. The high-speed results in the formation of an amorphous mixture that promotes chemical reactions. In the last decade, ball milling has gained importance as a green tool for the synthesis of organic frameworks in an environmentally friendly manner [51–54].

In 2015, Singh, Jang, and co-workers employed ionic liquid-coated ZnO nanoparticles for solvent-free synthesis of disubstituted benzimidazoles **(70)** via the reaction between *o*-phenylenediamine **(68)** with aromatic aldehydes **(69)** using the ball-milling technique (Scheme 18) [55].

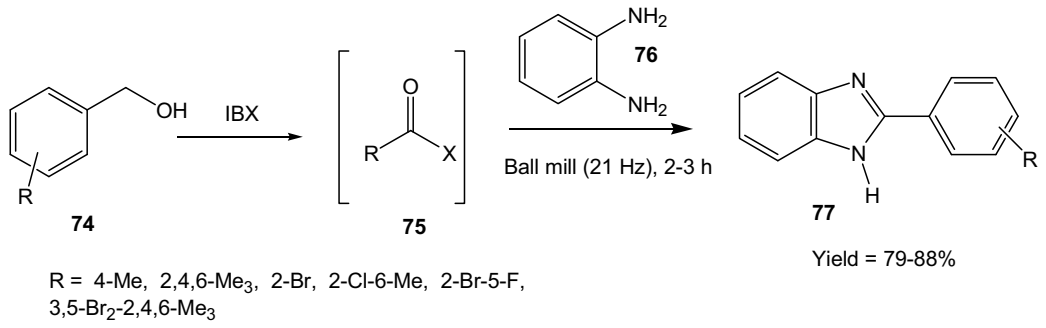
The methodology showed high yields of product, high turnover number, and high FT-IR frequency of the catalyst. The ball-milling technique helped avoid the use of toxic



Scheme 18: IL-ZnO nanocatalyst-catalysed synthesis of benzimidazoles under ball milling.



Scheme 19: Solvent and catalyst-free synthesis of benzimidazoles under ball milling.



Scheme 20: One-pot synthesis of benzimidazoles from benzyl alcohols and *o*-phenylene diamine under ball milling.

solvents, thus making the protocol environmentally benign. The reaction could also be reproduced at a multi-gram scale, which is an advantage for application in industries. The catalyst could be recycled six times without significant loss in catalytic activity.

Hagar and his group developed a ball-milling method for the synthesis of benzimidazoles **(73)** from the reaction between *o*-phenylene diamine **(71)** and organic electrophilic substrates **(72)** (Scheme 19) [56]. The reaction proceeded smoothly without any solvent or catalyst, thereby promoting sustainability. Several substituted aldehydes and carboxylic acids participated in the reaction to produce the corresponding benzimidazole derivatives in high yields.

The authors also extended the protocol to reactions between *o*-phenylene diamine and urea and thiourea to produce benzimidazol-2-one and benzimidazol-2-thione, respectively. Benzimidazol-2-thione is also produced when *o*-phenylene diamine is made to react with ammonium thiocyanate under identical ball-milling conditions. The reaction protocol is thus quite versatile, leading to a range of important organic moieties.

Mal and his group used IBX (2-iodoxybenzoic acid) as an oxidant for the conversion of substituted benzyl alcohols **(74)** into the corresponding benzaldehydes **(75)**, which then reacted with *o*-phenylene diamine **(76)** under ball milling to produce the corresponding benzimidazole derivatives **(77)** (Scheme 20) [57]. Benzyl alcohols with alkyl and halide substitutions participated in the reaction to produce the corresponding substituted benzimidazoles in reasonably high yields. The method involves solvent and catalyst-free one-pot synthesis of benzimidazoles, which makes the protocol environment-friendly.

5 Conclusions

Imidazole and its derivatives are important components in academic research laboratories and industries. Imidazoles constitute an important part of heterocyclic chemistry, and thus, development in the field of imidazole synthesis leads to a growth in heterocycle-based synthetic chemistry. In this review, we attempted to highlight the use and relevance of green tools like microwave irradiation, ultrasound irradiation, and ball milling for the synthesis of various imidazoles, benzimidazoles, and their derivatives.

Although the implementation of green tools in organic synthesis has a number of advantages, like low energy consumption, higher yields in shorter reaction time, and more sustainable reactions employing tandem one-pot and solvent-free processes, there are a few disadvantages as well. The major challenges associated with microwave- and ultrasound-irradiated reactions are the low chance of time-dependent monitoring and difficulty in scale-up reactions. Ball milling has its disadvantages of being very noisy and also poses contamination risks due to the occurrence of wear from the balls. All the green tool implemented protocols are expensive in nature overall, as a separate apparatus is required, which is yet another challenge. However, since green tools improve the sustainability of organic synthesis to a great extent, it should be the aim of future research scientists to eliminate or minimize the challenges associated with them.

Research is a dynamic process, and as such, research on sustainable methods of imidazole synthesis is constantly being updated. We tried to compile a few recent methodologies based on green tool-implemented imidazole synthesis, and we earnestly hope that this compilation will be useful for future research chemists who wish to work in the field of sustainable heterocycle synthesis.

Funding information: Authors state no funding involved.

Author contributions: Both D.S. and C. M. have contributed in writing and reviewing the manuscript. Both the authors have read and approved the final manuscript.

Conflict of interest: Authors state no conflict of interest.

Data availability statement: Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

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