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A COMPREHENSIVE REVIEW ON UTILIZATION OF VARIOUS METHOD IN THE SYNTHESIS OF IMIDAZOLE: METHODS AND STRATEGIES

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ABSTRACT

Imidazole is naturally occurring biomolecules known for their diverse biological activities like antibacterial activity, anticancer activity, antituberculosis activity, analgesic activity etc. It is a pivotal five-membered aromatic heterocycle, has garnered substantial attention in various domains, including medicinal chemistry, materials science, and beyond. This review encapsulates the conventional and most recent development in imidazole synthesis. It explores a spectrum of methodologies, encompassing classical routes, innovative strategies, and sustainable approaches. Additionally, this review emphasizes the biological significance and applications of synthesized imidazole's, underlining the necessity for proficient and eco-conscious imidazole synthesis. Imidazole, with its remarkable versatility, continues to captivate the interest of researchers and presents promising opportunities for diverse applications. The information presented in this comprehensive review article is poised to be an invaluable resource for researchers, clinicians, and pharmaceutical scientists. It will aid in the development of precise and highly biologically active imidazole derivatives, further advancing the field of medicine and pharmacology.

Keywords: Imidazole Synthesis, Classical Method Of Synthesis, Modern Strategies, Application, Biological Significance.

I. INTRODUCTION

Imidazole, recognized as a five-membered heterocyclic moiety, is characterized by the presence of three carbon atoms, two nitrogen atoms, four hydrogen atoms, and two double bonds. It is also commonly referred to as 1,3-diazole due to its structural composition. This heterocycle contains two nitrogen atoms, with one nitrogen atom bearing a hydrogen atom, while the other is referred to as the pyrrole-type nitrogen. The nomenclature "imidazole" was introduced by Arthur Rudolf Hantzsch (1857–1935) in the year 1887. Imidazole is amphoteric in nature, displaying both acidic and basic properties. It typically exists as a white or colorless solid and exhibits high solubility in water and other polar solvents. (1)

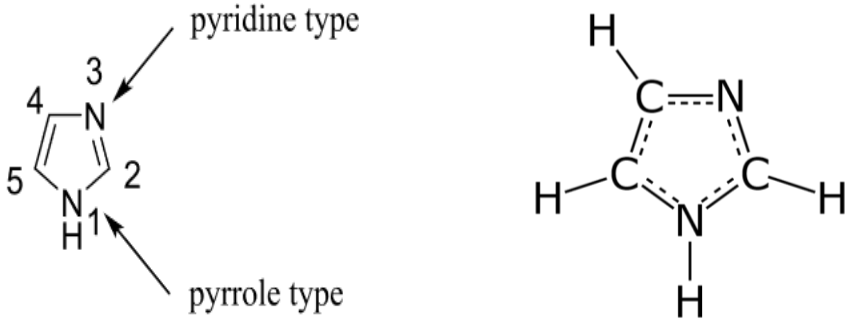

Fig 1. Structure of imidazole

Structure and properties- Imidazole, a planar 5-membered ring, exists in two equivalent tautomeric forms, a consequence of the ability to bind hydrogen to either of its nitrogen atoms. Notably, imidazole is a highly polar compound, illustrated by its substantial electric dipole moment measuring 3.67 D. It exhibits remarkable solubility in water, further highlighting its polar nature. Imidazole is classified as an aromatic compound, primarily due to the presence of a planar ring containing six π-electrons. This aromaticity arises from a pair of electrons originating from the protonated nitrogen atom and one electron from each of the remaining four

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atoms in the ring. Several resonance structures of imidazole further illuminate its intriguing electronic properties. (2)

Physical and Chemical properties- Imidazole is colorless liquid exhibits a notably high boiling point of 256°C, surpassing that of all other 5-membered heterocyclic compounds, owing to the presence of intermolecular hydrogen bonding, resulting in a linear association of molecules. imidazole are aromatic compounds, characterized by a resonance energy of 14.2 kcal/mol, which is nearly half of the value for pyrazole. Electrophilic substitution reactions are frequent in imidazole, while nucleophilic substitution reactions occur in the presence of electron-withdrawing groups within its nucleus. imidazole possesses a melting point of 90°C, demonstrating weak basicity and a tautomeric nature, as positions 4 and 5 are equivalent. Spectroscopic parameters for imidazole include a λmax of 207 nm, I.R. absorption bands at 1550, 1492, and 1451 cm^{-1}, and values for τ of 2.30 and 2.86. In mass spectroscopy, special attention is given to the study of heterocyclic compounds containing a single heteroatom, with less emphasis on those containing two or more heteroatoms. (3)

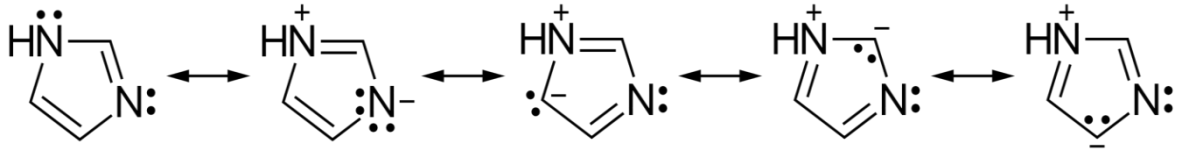

Fig 2.

Pharmacological activities- Imidazole derivatives exhibit a broad spectrum of pharmacological activities, as evidenced by a comprehensive literature survey. Research findings have indicated that imidazole and its derivatives are associated with various therapeutic properties, including analgesic and anti-inflammatory activity, cardiovascular effects, anti-neoplastic potential, antifungal properties enzyme inhibition capabilities, anti-anthelmintic activity, anti-filarial attributes, antiviral actions, and anti-ulcer potential. Beyond their remarkable pharmacological roles, these compounds also serve as versatile agents in other domains, functioning as dyestuffs, catalysts, and polymerization catalysts. (4)

- Antibacterial Activity- Vijesh et al. conducted an in-depth investigation into the in vitro antibacterial potential of newly synthesized compounds 1a–d and 2a–j. To evaluate their efficacy, a range of bacterial strains, including Escherichia coli, Staphylococcus aureus, Bacillus subtilis, Salmonella typhimurium, Clostridium perfringens, and Pseudomonas aeruginosa, were employed as test subjects. The antibacterial screening results unveiled that several of the tested compounds demonstrated significant inhibitory effects against the diverse spectrum of microbial strains. (5)
- Anticancer Activities- Baviskar et al. undertook a comprehensive study focusing on five distinct imidazole derivatives, each displaying remarkable catalytic inhibition of DNA. Notably, these compounds exhibited a heightened specificity towards Topoisomerase IIR, showcasing superior potency when compared to conventional chemotherapeutic agents such as Etoposide and 5-fluorouracil when tested on kidney cancer cells. (6)
- Anti-tuberculosis activity- In the year 2020, Koushik Mukherjee and colleagues from the University of Kalyani, India, conducted an extensive investigation into the efficacy of certain imidazole and piperidine derivatives against Mycobacterium smegmatis, with the aim of developing anti-tuberculosis drugs. These compounds not only augmented the efficacy of isoniazid and rifampicin when used in combination but also exhibited low cytotoxicity. Furthermore, their effectiveness against mycobacteria in a dormant state was assessed, revealing a significant impact on combating the pathogen. (7)
- Antifungal Activity - Yang and collaborators conducted a synthesis of various N-cyano-1H-imidazole-4-carboxamide derivatives and subjected them to fungicidal screening against six distinct fungi strains, including Fusarium oxysporum, Rhizoctonia solani, Botrytis cinerea Pers, Gibberella zeae, Dothiorella gregaria, and Colletotrichum gossypii, at a concentration of 50 μg/mL. Among these newly synthesized compounds, a notable trend emerged, showcasing their exceptional antifungal activity. Notably, compound 117h emerged as the most promising candidate, exhibiting an impressive EC50 value of 2.63 μg/mL against R. Solani. (8)

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- Analgesic Activity- In their research, Ucucu and colleagues detailed the synthesis of a series of 1-benzyl-2-substituted-4,5-diphenyl-1H-imidazole derivatives. To assess the analgesic properties, Swiss albino mice, spanning both sexes and weighing between 23–36 g, were utilized as test subjects. Interestingly, the findings revealed that the majority of the synthesized derivatives exhibited limited analgesic response. However, among them, compounds 138 and 139 demonstrated a moderate level of activity, while compounds 140 and 141 exhibited analgesic effects comparable to those of morphine, thus hinting at their potential as noteworthy candidates in the field of pain management. (9)
- Anti-HIV Evaluation- Researchers created various new compounds known as imidazole thioacetanilides and tested them to see if they could stop the human immunodeficiency virus type-1 (HIV-1). They found that compounds 148 and 145 were the most effective at inhibiting HIV-1, and several other compounds, including 146, 147, 149, and 144, also showed strong anti-HIV-1 properties. (10)

II. CONVENTIONAL METHODS FOR IMIDAZOLE SYNTHESIS

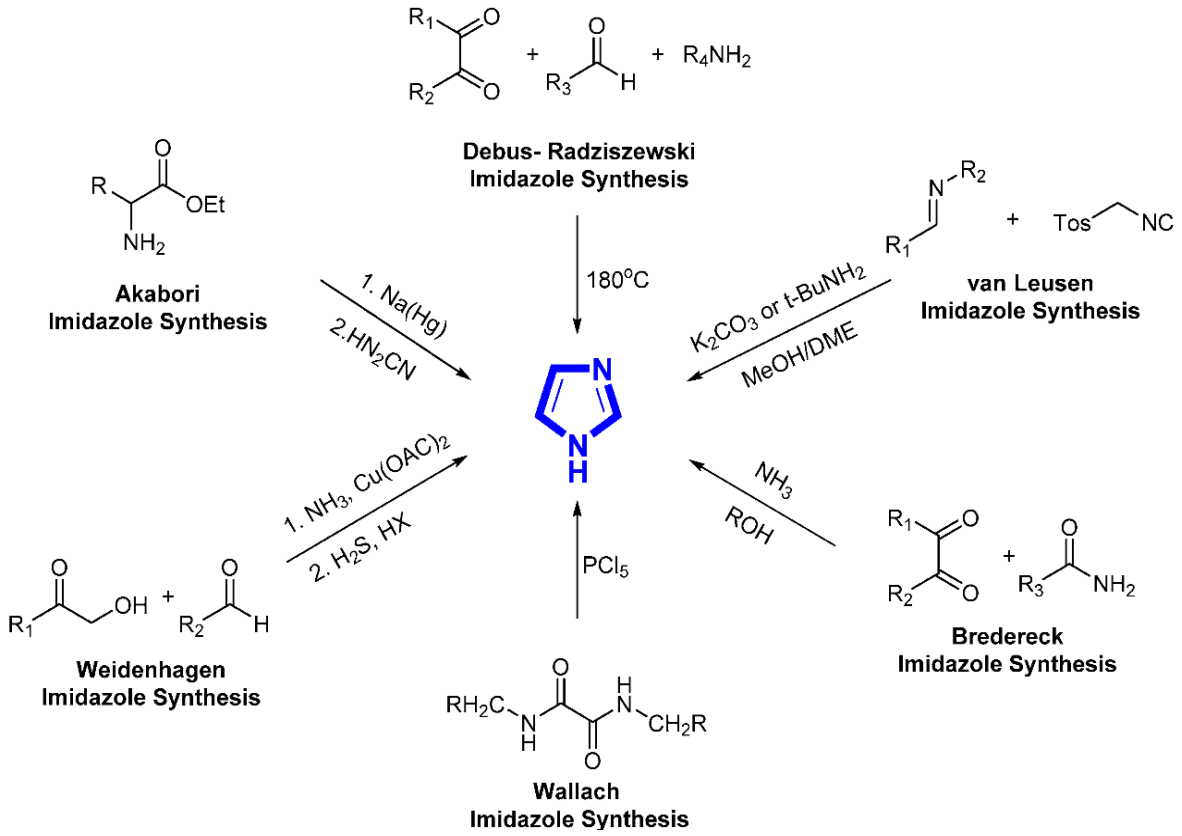

Fig 3. Typical synthetic methods for imidazole and its derivatives

The history of imidazole synthesis dates back to the 1850s, and over the past 165 years, a multitude of reactions and methods for constructing imidazole scaffolds have been meticulously documented. These include renowned methodologies such as the Debus–Radziszewski reaction, the Phillips–Ladenburg reaction, the Wallach reaction, the Weidenhagen reaction, the Bredereck reaction, the Akabori reaction, and the van Leusen reaction. However, despite their historical significance, many conventional synthesis methods still exhibit certain limitations, often characterized by harsh reaction conditions, prolonged reaction times, and less than satisfactory yields. (11)

Debus–Radziszewski imidazole synthesis-

The Debus–Radziszewski imidazole synthesis is a chemical reaction that creates imidazole using a 1,2-dicarbonyl, an aldehyde, and ammonia or a primary amine. This method is commonly used in industry to make various imidazoles. The process is an example of a reaction where multiple components come together. (12)

This reaction happens in two stages. In the first stage, the dicarbonyl and two ammonia molecules combine with the two carbonyl groups to form a diimine. (13)

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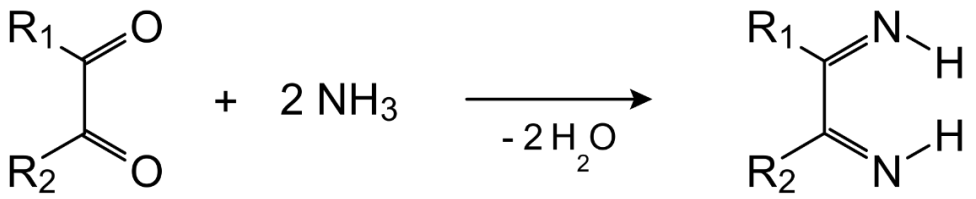

Fig 4.

In the second stage, this diimine condenses with the aldehyde:

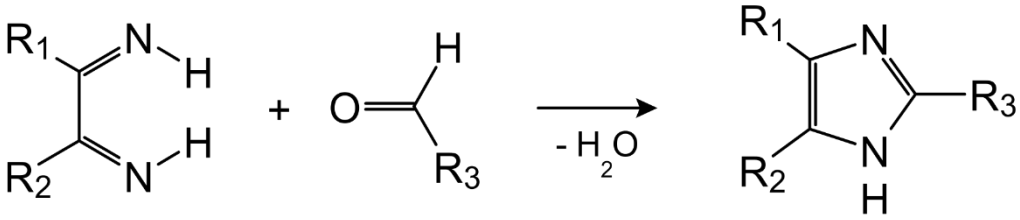

Fig 5.

- **van Leusen Imidazole Synthesis-**

In 1977, van Leusen and colleagues reported that a reaction involving TosMIC and aldimine could create a new compound in the presence of a base in a solution containing protons. They also studied how the chemical groups R1 and R2 influenced the formation of a specific compound, known as 1,4,5-trisubstituted imidazoles. They found that using α-tosylbenzyl isocyanate and α-tosylethyl isocyanate could lead to the creation of these imidazoles. This reaction is now widely known as the van Leusen imidazole synthesis, recognized for its numerous benefits. (14)

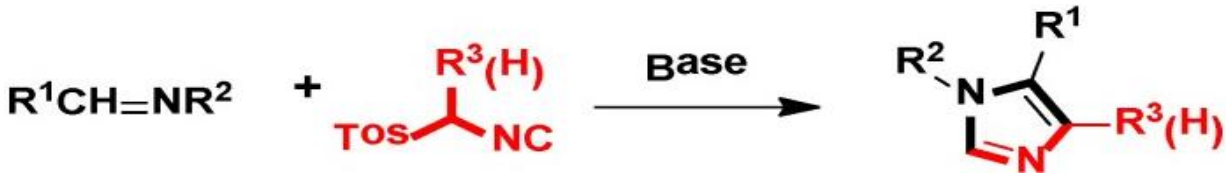

Fig 6.

- **Bredereck Imidazole Synthesis-**

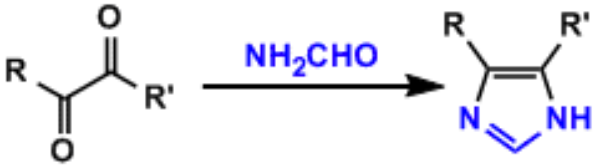

Fig 7.

The Bredereck synthesis, sometimes called the Bredereck imidazole synthesis, is an important reaction in organic chemistry. It was introduced by the German chemist Hellmut Bredereck in 1953. This reaction is employed to create 4,5-disubstituted imidazoles, a type of chemical compound. The reaction typically proceeds in two stages, with the initial stage involving the condensation of the dicarbonyl and ammonia to form a diimine. The diimine then reacts with an aldehyde in the second stage, resulting in the formation of imidazoles.

This reaction is a useful tool in organic synthesis for creating imidazoles, which have various applications in chemistry, pharmaceuticals, and materials science. (15)

- **Wallach imidazole synthesis-**

The reaction involving N-benzylamides of N-heterocyclic carboxylic acids with phosphorus pentachloride results in the production of heterocondensed imidazoles. This process is reminiscent of Wallach's imidazole synthesis that begins with N, N′-dialkyloxamides. The study includes kinetic experiments and labeling techniques that support a mechanism involving nitrite ylide species, shedding light on the Wallach reaction. The electron availability of the heterocyclic ring is a critical factor influencing the formation of these heteroanellated imidazoles. (16)

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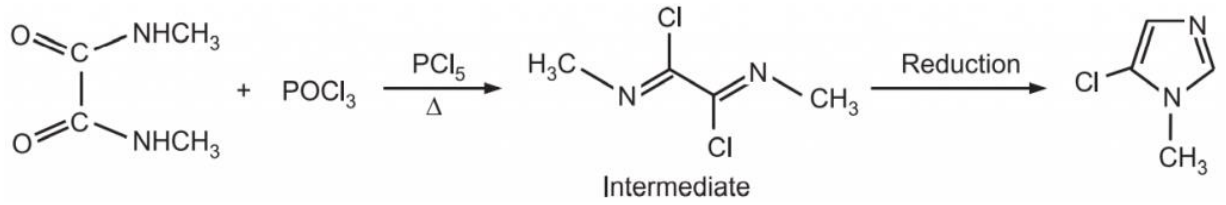

Fig 8.

- **Marckwald imidazole synthesis-**

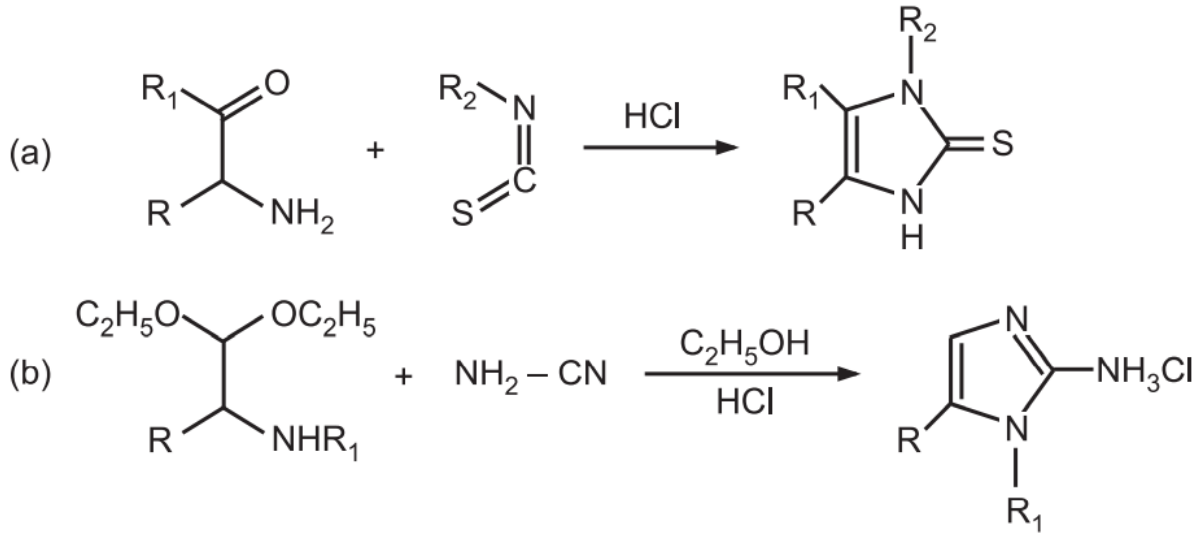

Fig 9.

The Marckwald synthetic method is used to create 2-mercaptoimidazoles by starting with α-amino ketones or aldehydes and potassium thiocyanate, resulting in 2-thiol substituted imidazoles. The sulfur component can be easily removed using various oxidative techniques, yielding the desired products with up to 86.97% efficiency. (17)

- **From α- Halo Ketone-**

This method relies on the interaction between alpha halo ketones and imidine. It has been effectively used to produce 2,4- or 2,5-biphenyl imidazoles. Additionally, acyloin can react with amidine or alpha halo ketones to form imidazoles. (18)

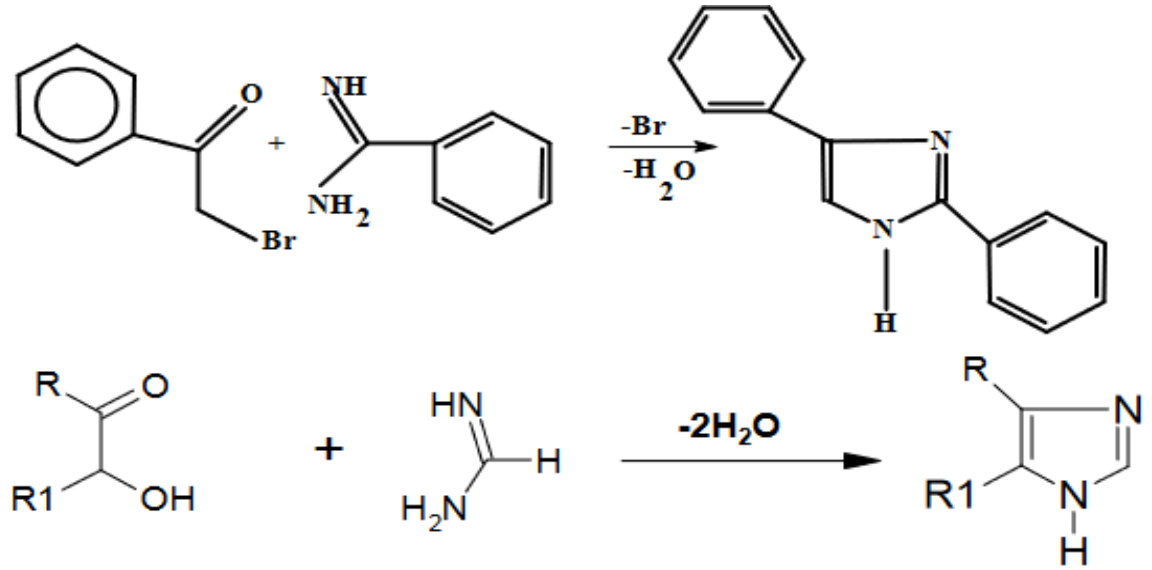

Fig 10.

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- **From aminonitrile and aldehyde-**

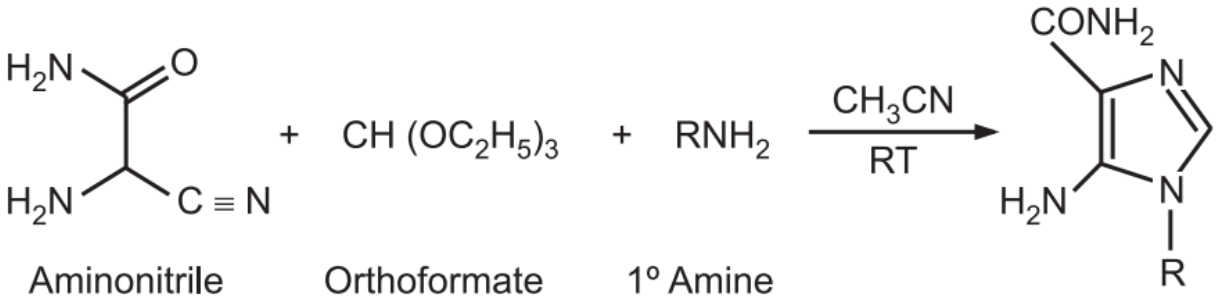

Fig 11.

Mixture of an aldehyde and aminonitrile on condensation under suitable conditions gives substituted imidazoles. (19)

- **From dehydrogenation of imidazoline-**

Knapp and their team have introduced a gentler reagent, barium permanganate (BaMnO4), which facilitates the transformation of imidazolines into imidazoles in the presence of sulfur. When imidazolines, derived from alkyl nitriles and 1,2-ethanediamine, are treated with BaMnO4, they result in the formation of 2-substituted imidazoles. (19)

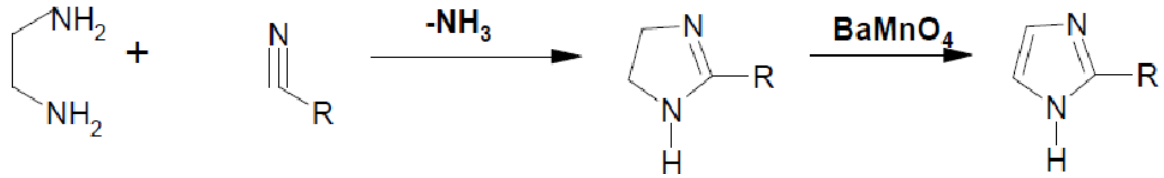

Fig 12.

III. MODERN METHODS OF IMIDAZOLE SYNTHESIS

- **Hopfl et al (2005)**

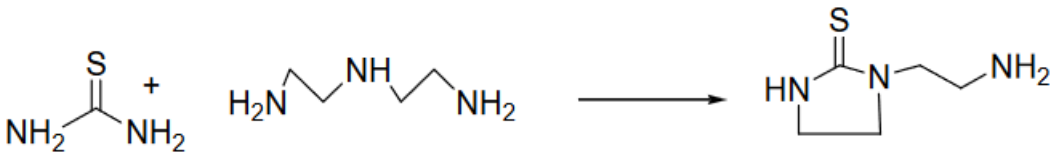

Fig 13.

A detailed account of the synthesis of 1-(2-aminoethyl)-2-imidazolidinethione (5 was provided, and the crystal and molecular structure of the compound were successfully determined. By combining X-ray crystallography and theoretical calculations using DFT, researchers gained valuable insights into the compound's exceptional performance as a low-toxicity corrosion inhibitor. (20)

- **Tenhave et al. (1197)**

A process for making 4(5)-monosubstituted imidazoles has been developed by using a base-induced cycloaddition of tosylmethyl isocyanide (TosMIC) to N-(dimethylsulfamoyl) aldimines or N-tosylaldimines. When reacting with N-(dimethylsulfamoyl) aldimines, the initial products are N-(dimethylsulfamoyl) imidazoles, and the dimethylsulfamoyl group can be easily removed with aqueous HBr. In the case of N-tosylaldimines, the tosyl group is spontaneously lost, resulting in the formation of 4(5)-monosubstituted imidazoles in a single step. (21)

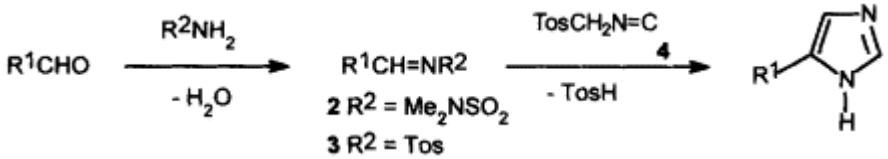

Fig 14.

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Sharma et al. (2008)

Sharma and their team have outlined a method for creating 2-substituted-1H-imidazole derivatives. This involves the reaction of ethylenediamine with an acid chloride in dry dioxane at room temperature, resulting in the production of the corresponding amide. The amide then undergoes cyclization with boron trifluoride etherate (BF3.OEt2), yielding significant yields of the 2-substituted-1H-imidazole derivatives. These compounds exhibited activity against various bacteria, including E. coli, S. Typhimurium, B. subtilis, and S. aureus. Notably, these reactions occurred under relatively mild conditions and provided the desired products in good yields. (22)

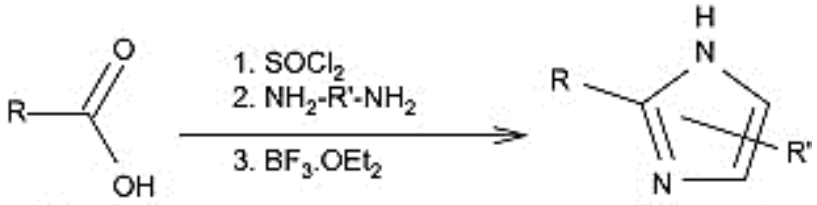

Fig 15.

Maruthikumar et al. (2005)

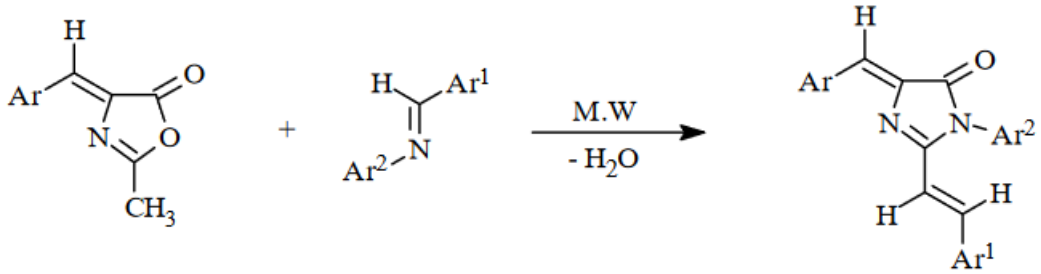

Fig 16.

Maruthikumar and colleagues introduced a novel method for creating a specific motif known as 1-aryl-2-(1E)-arylvinyl-4-arylmethylene-2-imidazoline-5-ones. This was achieved through condensation reactions involving 4-arylidene-2-methyl-2-oxazoline-5-one and a suitable Schiff base, facilitated by microwave irradiation. The result of this reaction is the production of 1-aryl-2-(1E)-arylvinyl-4-arylmethylene-2-imidazolin-5-ones. (23)

Behrouz group et al. (2020)

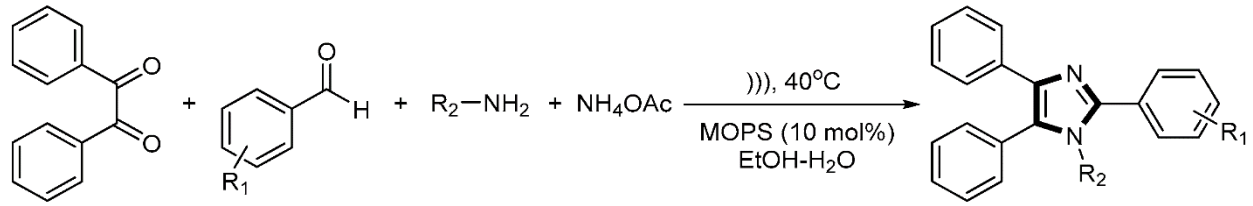

Fig 17.

The Behrouz group introduced a new method for efficiently producing 2,4,5-trisubstituted imidazole, utilizing the catalytic properties of triphenylphosphine (PPh3) and ultrasound assistance. They discovered that PPh3 was an effective catalyst for the D–R reaction at room temperature, offering an eco-friendly approach with an affordable and safe catalyst for synthesizing compound. Notably, they used urea as the nitrogen source, which yielded higher product yields (up to 95%) compared to using NH4OAc (up to 87%). This method resulted in excellent yields of imidazole derivatives ranging from 80% to 95%. (24)

Damavandi et al. (2011)

Damavandi developed a convenient one-step method for producing 2-aryl-1H-phenanthro[9,10-d] imidazoles using ultrasonic irradiation, as outlined in Scheme. In their quest for the most suitable catalyst to facilitate the condensation of aldehydes, 9,10-phenanthrenequinone, and ammonium acetate, researchers explored various organic acids and their salts. The best results, with a yield of 94%, were achieved when ultrasonic irradiation and p-toluenesulfonic acid (p-TSA) were used as the catalyst, with ethanol as the solvent. This p-TSA-catalyzed

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approach offered a straightforward and efficient method for synthesizing, making purification a straightforward process. (25)

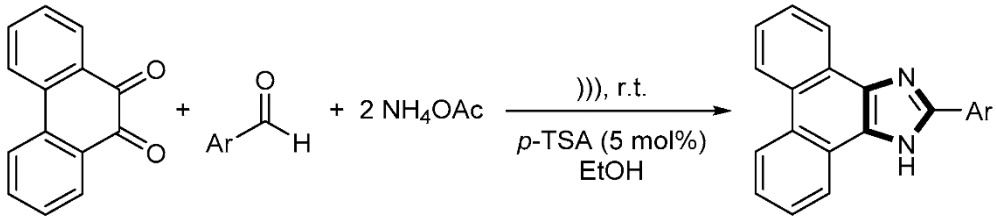

Fig 18.

- **Khosropour et al (2008)**

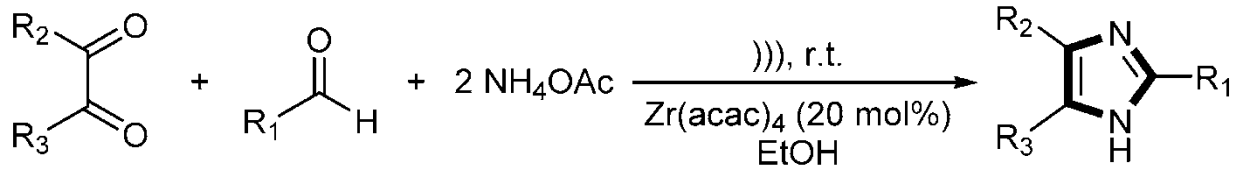

Fig 19.

Khosropour and their team introduced a straightforward and environmentally friendly method for creating 2,4,5-trisubstituted imidazole, using zirconium (IV) acetylacetonate (Zr(acac)4) as the catalyst and starting materials including aldehydes, benzils, and ammonium acetate, as illustrated in Scheme. This method achieved the highest yield of 97%. Compared to traditional reflux reactions, which took around 3 hours with a maximum yield of 84%, these ultrasonic-assisted reactions were typically completed in just 20 to 50 minutes, offering a significant time-saving advantage. (26)

- **Hajizadeh et al (2020)**

Hajizadeh and her team devised a one-pot, three-component reaction using an innovative and environmentally friendly NiFe2O4-geopolymer nano-catalyst to synthesize imidazole derivatives, with the aid of ultrasonic irradiation. The nano-NiFe2O4 supported on geopolymer proved to be an excellent catalyst, surpassing the performance of other catalysts such as bentonite, geopolymer, and NiFe2O4 nanoparticles. Additionally, it demonstrated stable recyclability, making it an efficient and sustainable choice for this chemical reaction. (27)

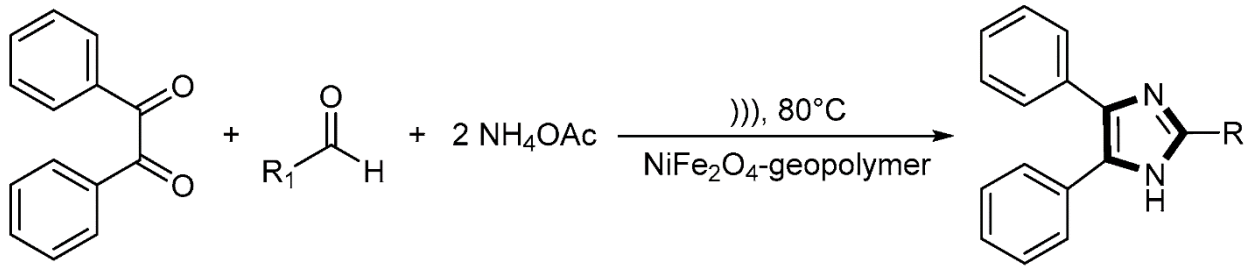

Fig 20.

Biological significance and applications of synthesized imidazole's:

Imidazole compounds have a wide range of applications, from pharmaceuticals to agrochemicals and materials science. This section outlines the significance of efficient synthetic methods for these diverse fields.

- Imidazole plays a significant role in various biological molecules, with histidine being a notable example, featuring an imidazole side chain. Histidine is a key component of many proteins and enzymes and is crucial for the structure and binding functions of hemoglobin.
- It can also undergo decarboxylation to produce histamine, a common biological compound that is involved in allergic reactions like urticaria.

- In the field of protein purification, imidazole is utilized in immobilized metal affinity chromatography (IMAC) to isolate His-tagged proteins. When an excess of imidazole is introduced, it displaces the His-tag from the nickel-coordination sites, releasing the His-tagged proteins.
- Imidazole has found its way into the pharmaceutical industry, playing a role in various medications, including antifungal, antiprotozoal, and antihypertensive drugs. It's a component of theophylline, which is found in tea and coffee and acts as a central nervous system stimulant.
- Additionally, imidazole is present in the anticancer medication mercaptopurine, which disrupts DNA activities to combat leukemia.
- Imidazole, on its own, has limited direct applications. However, it serves as a precursor for a wide range of agrichemicals, including compounds like enilconazole, climbazole, clotrimazole, prochloraz, and bifonazole. These derived substances are important in various agricultural and pharmaceutical applications.
- Several substituted imidazoles, clotrimazole among them, are known as selective inhibitors of nitric oxide synthase. This characteristic makes them intriguing prospects for drug development in the context of inflammation, neurodegenerative diseases, and nervous system tumors. Additionally, the imidazole pharmacophore is associated with various biological activities, including the downregulation of intracellular Ca2+ and K+ fluxes, as well as interference with translation initiation processes. These properties contribute to their potential therapeutic applications. (28,29,30)

IV. CONCLUSION

In conclusion, this comprehensive review has provided a detailed and insightful exploration of the diverse methods and strategies employed in the synthesis of imidazole, a versatile and important heterocyclic compound. We have covered a broad spectrum of synthetic approaches, ranging from classical methods to modern and innovative techniques, showcasing the ever-evolving landscape and biological significance and applications of synthesized imidazole's. This comprehensive review serves as a valuable resource for researchers, scientists, and students in the field of chemistry, providing a deep understanding of the various methods and strategies available for imidazole synthesis. It is our hope that this review will inspire further research and innovation in this area, ultimately leading to the development of novel imidazole-based compounds with broader applications and benefits for society.

ACKNOWLEDGMENTS

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V. REFERENCE

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