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A Comprehensive Study on Synthesis of Benzimidazole using Novel Techniques

Manal M. Iqbal Takey and Mehreen M. Dawre

D.G. Tatkare Mahavidyalay, Mangaon- Raigad, Maharashtra

Abstract: *Benzimidazoles are a class of heterocyclic compounds in which a benzene ring is fused to the 4 and 5 positions of an imidazole ring. Benzimidazole refers to the parent compound, while benzimidazoles are a class of heterocyclic compounds having similar ring structures, but different substituents. Green chemistry is the new and rapidly emerging field of chemistry. It involves the utilization of a set of principles that reduces or eliminates the use or generation of Hazardous substances in the design, manufacture and application of chemical products. Conventional methods of synthetic reactions need longer heating time, elaborate and tedious apparatus set up which result in higher cost and environmental pollution in Contrast to greener methods which are eco-friendly and economical. In Recent years, a large number of reports related to synthesis of Nitrogen, Oxygen and Sulphur containing heterocyclic have appeared owing to a wide variety of their biological Activity. In recent years, numerous reports concerning the synthesis of heterocyclic compounds under various conditions like solvent-free, reactants immobilized on solid Support, microwave irradiation condition, green catalyst and green solvent have appeared. Benzimidazole is a heterocyclic aromatic organic compound, it is an important Pharmacophore and privileged structure in medicinal chemistry. It plays a very important role with plenty of rational therapeutic activities such as antiulcer, antihypertensive, analgesic, Anti-inflammatory, anti-viral, antifungal, anticancer, and antihistaminic. Because of its Importance, the methods for their synthesis have become a focus of Synthetic Organic Chemists. Therefore, in the present work I tried to organize the chemistry of different Derivative of substituted benzimidazole and some of the important methodologies used for the Synthesis.*

Keywords: Benzimidazole, Eco-Friendly, Solvent free, green synthesis, Microwave Assisted, Catalysis.

I. INTRODUCTION

Benzimidazole derivatives are particularly important compounds due to the wide variety of biological activities and therapeutic applications they have, as well as their powerful restricting action and excellent property magnitude relation [1]. Benzimidazole derivatives also have an excellent property magnitude relation. In light of the significance of benzimidazole, it was decided to devise and produce a variety of novel benzimidazole derivatives, each of which would consist of an oxadiazole moiety [2]. The possible biological activity of these chemicals would next be investigated in order to determine whether or not they had any of that potential. In the field of study pertaining to pharmaceuticals, the benzimidazole ring is an important part of the heterocyclic pharmacophore [3]. Compounds with a variety of substituents in the benzimidazole structure have been linked to a wide range of biological effects, including antibacterial, anticancer, antiviral, antioxidant, antifungal, helminthicidal, histamine-blocking, anticoagulant, and antihypertensive effects [4]. These effects have been attributed to the compounds. The benzimidazole ring is generally recognised as a key pharmacophore at this point in time within the context of modern day drug development. When it comes to health-related research, the synthesis of new benzimidazole derivatives is still regarded as an important area of focus for academic inquiry [5].

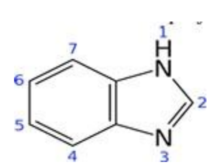

Fig. 1: Structure of Benzimidazoles

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1.1 Physical Properties Of Benzimidazoles

It would seem, on the basis of the melting points of several benzimidazoles, that exchanging the 1-position results in a lower melting point the vast majority of the time. Polar solvents have a greater capacity than organic solvents for the dissolution of benzimidazoles containing imide nitrogen [6]. The solubility of the molecule might potentially be improved in liquids that are non-polar if additional non-polar substituents are inserted at different other places on the benzimidazole ring. In contrast, the presence of polar groups inside the molecule causes an increase in its solubility in polar liquids. This effect may be seen in both aqueous and aqueous solutions [7]. In general, benzimidazoles are soluble in mild acids and have a moderate basicity, which means that they are somewhat less basic than imidazole. This is because benzimidazoles have a benzene ring structure instead of an imidazole ring structure [8]. This is due to the fact that benzimidazoles are a kind of derivative derived from imidazole. Benzimidazoles are generally soluble in alkaline solutions, despite the fact that their high level of acidity renders them prone to the production of N-metallic compounds when they are dissolved in water [9]. Similar to the situation with imidazole, it would seem that resonance-based ion stabilisation is to blame for the acidic characteristics of benzimidazoles. The dissolution of the more acidic benzimidazoles may be possible with a solution that is less basic, such as one that includes potassium carbonate. This is because there is a possibility that such a solution will contain potassium carbonate [10].

1.2 Chemical Properties of Benzimidazole

Reactions of the benzimidazole ring: The benzimidazole ring is distinguished by a high level of stability as a defining characteristic. It makes no difference whether the benzo(a)imidazole is subjected to alkalis, hot hydrochloric acid, or intense sulfuric acid; its characteristics do not alter in any way. [11]. Oxidation is a process that may break the benzene ring of benzimidazole, but only under very specific conditions. The benzimidazole ring is only able to tolerate decrease in its structure under certain circumstances.

1.3 Common Methods of Synthesis:

Several strategies have been developed to facilitate the acylation of amines, each with its unique Advantages and limitations. The four primary methods include:

1.3.1-Traditional method of synthesis of benzimidazole:

Preparation of benzimidazoles practically starts with benzene derivatives possessing nitrogen-containing Functions ortho to each other i.e. the starting material o –Phenylenediamines (OPD) react readily with most Carboxylic acids to give 2-substituted benzimidazoles, usually in very good yield. The reaction is carried Out usually by heating the reactants together on a steam bath, by heating together under reflux or at an elevated Temperature, or by heating in a sealed tube [12].

1.3.2- Microwave Assisted Synthesis:

Microwave-assisted synthesis offers a greener alternative by significantly reducing reaction Times and improving reaction efficiency. The method is known for its ability to provide uniform Heating, which leads to faster reactions with higher yields and energy savings. Microwave-assisted synthesis of benzimidazole from o- phenylenediamine and Aldehydes in the presence of solid acid catalysts has shown accelerated reaction times and high yields compared to conventional heating [13].

1.3.3-Solvent-Free Synthesis:

Green solvents, such as water, ethanol, or ionic liquids, are increasingly being employed for the synthesis of benzimidazole to minimize the use of toxic organic solvents. Water, being an Abundant, non-toxic, and non-volatile solvent, is the most sustainable option, particularly for Reactions that can be carried out under mild conditions. Synthesis of benzimidazole in water or ethanol using catalytic amounts of ionic liquids or sulfonic acid-functionalized resins has been reported with high yields and minimal Side reactions [14].

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1.3.4-Catalytic Methods:

Using efficient and recyclable catalysts is a key feature of green chemistry. Solid acid catalysts, Metal-based catalysts, and ionic liquids are commonly used for the catalytic synthesis of Benzimidazole, enhancing the reaction's atom economy and minimizing waste production. Solid acid catalysts like zeolites or montmorillonite clay have been shown to Catalyzed The synthesis of benzimidazole from o-phenylenediamine and various electrophilic Reagents, offering high selectivity, simple recovery, and reusability [15].

II. APPLICATIONS

2.1-Medicinal chemistry

Benzimidazole and its derivatives hold significant importance in medicinal chemistry due to their broad- spectrum pharmacological activities, making them key structural components in many therapeutic drugs. They exhibit antimicrobial, antifungal, antiviral, anticancer, anti-inflammatory, and anthelmintic properties, leading to their widespread use in pharmaceuticals. Several benzimidazole-based drugs, such as albendazole, mebendazole, and thiabendazole, are widely used as anthelmintics to treat parasitic infections [16]. Additionally, omeprazole, pantoprazole, and lansoprazole, which are proton pump inhibitors (PPIs), contain benzimidazole cores and are extensively prescribed for gastric ulcers and acid reflux disorders. Some benzimidazole derivatives also exhibit antitumor activity by inhibiting microtubule polymerization or targeting specific cancer-related enzymes, making them valuable in chemotherapy. Furthermore, benzimidazole scaffolds are being explored for antiviral applications, including potential treatments for HIV, hepatitis, and coronaviruses. Their high bioavailability, chemical stability, and diverse biological activities make benzimidazole derivatives indispensable in modern drug discovery and development [17].

2.2-Material Science:

Benzimidazole and its derivatives find diverse and significant applications due to their unique structural and electronic properties. These compounds are employed in the development of functional materials with tailored characteristics. For instance, benzimidazole-based molecules are utilized in the creation of advanced polymers and coatings, enhancing their thermal stability, mechanical strength, and chemical resistance. Furthermore, they serve as crucial components in the synthesis of organic semiconductors, contributing to the development of organic light-emitting diodes (OLEDs) and organic solar cells [18] . The presence of the nitrogen atoms within the benzimidazole ring allows for coordination with metal ions, making these compounds useful in the design of metal-organic frameworks (MOFs) with potential applications in gas storage, separation, and catalysis. Additionally, benzimidazole derivatives are explored in the creation of photochromic materials, which can change their optical properties upon exposure to light, finding use in smart windows and optical data storage. Their ability to interact with various surfaces also makes them relevant in the development of corrosion inhibitors for metals, protecting them from degradation. Overall, the versatility of benzimidazole in forming stable and functional materials positions it as a valuable building block in various advanced material applications [19].

2.3-Agrochemicals:

Benzimidazole and its derivatives play a crucial role in agrochemicals, particularly as fungicides, pesticides, and plant growth regulators. Due to their broad-spectrum biological activity, they are widely used to protect crops from fungal diseases and pests, ensuring higher agricultural yields. Benzimidazole-based fungicides, such as carbendazim, thiophanate-methyl, and benzoyl, effectively control various fungal pathogens affecting crops like wheat, rice, fruits, and vegetables by inhibiting microtubule formation in fungal cells, preventing their growth and reproduction [20]. Additionally, some benzimidazole derivatives exhibit insecticidal and nematicidal properties, helping in the management of pests like aphids and nematodes. Beyond pest control, certain benzimidazole compounds also function as plant growth regulators, enhancing crop resistance to environmental stress and improving overall plant health. Their effectiveness, low toxicity to mammals, and stability make them indispensable in modern sustainable agriculture. However, their overuse can lead to resistance in pathogens, necessitating responsible application and rotation with other fungicides [21].

2.4-Dyes and Pigments:

Benzimidazole derivatives are widely used in the production of dyes and pigments due to their excellent thermal stability, photostability, and vibrant coloration. These compounds serve as key intermediates in the synthesis of organic pigments, particularly in high-performance pigments (HPPs) used for coloring plastics, textiles, coatings, and inks. Benzimidazolone pigments, a prominent class of benzimidazole-based colorants, exhibit superior lightfastness, chemical resistance, and durability, making them ideal for industrial applications such as automotive coatings and high-quality printing inks [22]. Additionally, benzimidazole-based fluorescent dyes are employed in biological staining, textile dyeing, and optoelectronic devices due to their strong luminescent properties. The structural versatility of benzimidazole allows for the development of dyes with tunable color shades, ranging from yellow to deep red, further enhancing their commercial significance in the pigment industry [23].

2.5-Food Industry:

Benzimidazole derivatives play an important role in the food industry, primarily as preservatives, antioxidants, and food color stabilizers. Some benzimidazole-based compounds exhibit antimicrobial properties, helping to extend the shelf life of perishable foods by preventing microbial contamination [24]. Additionally, certain benzimidazole derivatives function as antioxidants, protecting food products from oxidative degradation and preserving their nutritional value and sensory qualities. In food packaging, benzimidazole-based materials are used to enhance the durability and stability of packaging films, reducing spoilage and maintaining food freshness. Furthermore, some benzimidazole-based dyes are utilized in food coloring applications, offering high stability and resistance to light and heat [25].

III. FUTURE OPPORTUNITIES AND DIFFICULTIES

The green synthesis of benzimidazole presents exciting future opportunities as researchers aim to develop more eco-friendly, cost-effective, and sustainable methods for its production. Benzimidazole synthesis using green chemistry holds great promise, with advancements in biodegradable catalysts, solvent-free methods, and renewable feedstocks offering more sustainable and eco-friendly alternatives. Emerging techniques like microwave-assisted synthesis, nanocatalysis, and deep eutectic solvents (DESs) can enhance efficiency while reducing waste and energy consumption. However, challenges such as the high cost of green catalysts, scalability issues, and difficulties in catalyst recovery must be addressed for industrial adoption.

3.1 Biodegradable Catalysts: One of the key future directions is the development of biodegradable, environmentally friendly catalysts that can replace traditional toxic or precious metal catalysts. These catalysts could reduce the environmental burden of the synthesis process by minimizing the need for complex waste disposal techniques. Additionally, new catalytic systems could offer improved selectivity and efficiency, thereby enhancing reaction yields and reducing waste generation. Research into biocatalysts and enzyme-driven reactions holds particular promise in this area, potentially revolutionizing the synthesis of benzimidazole with minimal environmental impact.

3.2 Solvent-Free Methods: The move towards solvent-free synthesis is a growing trend in green chemistry. By eliminating or significantly reducing the use of solvents, which are often harmful to the environment, researchers aim to create more sustainable production processes. In benzimidazole synthesis, solvent-free approaches can not only minimize hazardous chemical waste but also reduce energy consumption since solvent removal processes can be energy-intensive. Techniques such as mechanochemical reactions, where reactions are driven by physical energy (e.g., grinding or mixing), could be further developed for green synthesis routes.

3.3 Renewable Feedstocks: The use of renewable feedstocks, such as biomass or bio-based intermediates, is another key area for green benzimidazole synthesis. Utilizing renewable resources instead of petrochemical derivatives reduces the reliance on fossil fuels and supports the transition to a circular economy. Advancements in biotechnology could lead to the development of bio-based precursors that enable more sustainable and cost-effective production of benzimidazole.

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3.4 Microwave-Assisted Synthesis: Emerging technologies like microwave-assisted synthesis have the potential to significantly enhance the efficiency of benzimidazole production. By using microwave energy to accelerate reactions, this technique can reduce reaction times, energy consumption, and the formation of unwanted byproducts. Further optimization of microwave-assisted processes could lead to greener, faster, and more efficient production methods for benzimidazole.

3.5 Nanocatalysis: The use of nanomaterials in catalysis offers exciting possibilities for green benzimidazole synthesis. Nanocatalysts, with their high surface area and tunable properties, can provide higher catalytic efficiency, allowing reactions to occur under milder conditions and with fewer byproducts. The incorporation of nanocatalysis could also enable the reuse and recycling of catalysts, reducing the environmental impact and cost of the synthesis process.

IV. CONCLUSION

The synthesis of benzimidazole using green chemistry principles offers a promising pathway Toward more sustainable, efficient, and environmentally friendly chemical processes. As a key Compound in pharmaceuticals, agrochemicals, and material science, benzimidazole plays Critical role in many industries, making its synthesis a focal point for green chemistry Innovations. In conclusion, the synthesis of benzimidazole using green chemistry not only enhances the Efficiency and sustainability of chemical production but also aligns with broader environmental and societal goals. By embracing these greener techniques, the chemical industry can reduce Its environmental impact while maintaining or even improving the performance and yield of Benzimidazole, contributing to the overall advancement of sustainable chemistry. The transition to green chemistry in the synthesis of benzimidazole marks a critical step Toward creating more sustainable, safer, and efficient chemical processes in various industries. As benzimidazole derivatives are integral to the pharmaceutical, agrochemical, and material Sciences, employing green chemistry principles is not only important for reducing Environmental harm but also for ensuring the long-term sustainability of these industries. The Future of benzimidazole synthesis lies in harnessing these innovative green methodologies to Address the growing demand for eco-friendly processes and reduce the ecological footprint of Chemical manufacturing. In conclusion, the synthesis of benzimidazole using green chemistry is not just a forward-Thinking concept but a crucial pathway to meeting the evolving demands of sustainable Chemical processes. In Conclusion, the synthesis of benzimidazole using green chemistry is an essential step toward a more sustainable and economically viable future. By capitalizing on greener alternatives and cutting-edge technologies, the chemical industry can contribute to a circular economy, improve process efficiency, and reduce the environmental and economic impacts traditionally associated with chemical manufacturing. As research and innovation in this field continue to evolve, the future of benzimidazole synthesis is poised to become a shining example of how green chemistry can drive significant change across various industries, enhancing both environmental stewardship and industrial performance.

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