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Review article

Green Synthesis of Benzimidazole Derivatives: an Overview on Green Chemistry and Its Applications



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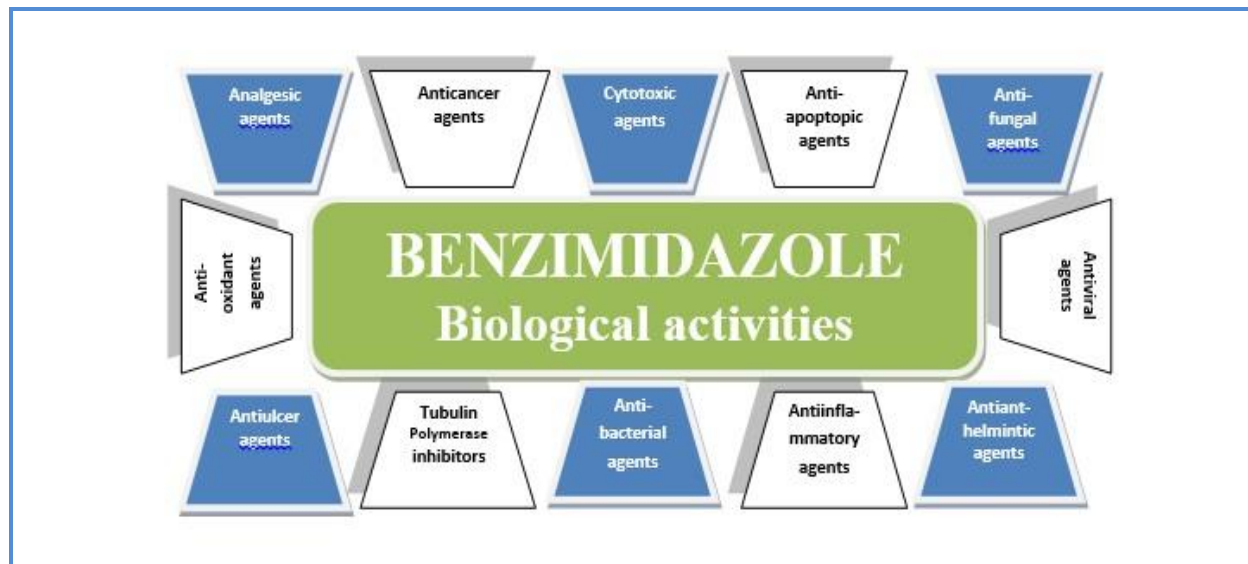
KEYWORDS

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ABSTRACT

The chemical substances in our environment are rising day by day. Only some of them are degraded, but most of them are non-degradable. These non-degradable substances produce pollutions which cause instability, harm or discomfort to the ecosystem as pollutions and create a risk to the environment. To reduce the possibility of a system we must reduce the risk not by altering the effect but by the cause. Thus, green chemistry (GC) concept was introduced, and it is a rapidly emerging field of chemistry. The GC is the design of chemical products and procedures that decrease or remove the use and production of harmful substances. In recent years, various heterocyclic compounds have appeared owing to the extensive varieties of their pharmacological activities. Benzimidazole is a heterocyclic aromatic compound. It is a vital and advantaged structure in medicinal chemistry and plays a role with ample therapeutic activities like analgesic, anti-inflammatory, antiulcer, antihypertensive, antibacterial, antiviral, antifungal, anticancer and antihistaminic. Because of its value, the processes for their synthesis have become a focus of synthetic chemists. Therefore, this review aims at compiling the chemistry of differently substituted benzimidazoles and some other methods. Conventional methods of synthesis need longer heating time, complicated and tedious apparatus set up which result in high cost and pollution in contrast to greener methods which are inexpensive.

Graphical Abstract



Introduction

Green chemistry (GC) is an invention, design, and application of chemical products and procedures to decrease or to abolish the use and creation of hazardous substances for the living environments. The GC starts with the theory of design and looks for the kind of product and also how we are going to design its manufacturing and uses. The impact of chemical compounds and chemical methods must be considered as design criteria. Hazard concerns for early material and final products must also be included in the performance criteria. From the start of the 1990s, the ideas of GC started to have a more global view. The purpose was to initiate an option carried out in the chemical industry and procedures more benign to the environment. A committee of experts was convened from many industrial countries to advise the areas of research and development for GC applications. The areas proposed for focus under the GC values were the following. They were selected with an emphasis on economic concerns and for their future input to sustainable development [1-5].

Focused areas under green chemistry principles

Use of alternative feedstocks

There are already many novel progresses in this field, but the emphasis on renewable raw products and a shift from fossil fuels are very desirable for sustainability. The starting products for the chemical industries must be renewable and less hazardous for workers and the corresponding environment [6-10].

Use of less hazardous reagents

There are enough data for the toxicological and ecotoxicological properties of most of the high amount of chemicals used for industries. Chemists must divert their efforts to use less hazardous raw materials and chemical reagents for the synthetic ways of the production of chemical compounds. However, if there are main obstacles they must choose less compounds and alter their techniques, for example, the use of catalysts and new synthetic methods.

Use of natural processes like biocatalytic techniques

New biosynthesis which were developed in the last decade were more selective, and used low energy, low temperatures, and high yields and demanded raw chemicals which are less toxic. Green chemistry (GC) research replaced many old methods and introduced some novel catalytic with high yields and fewer waste products.

Use of alternative solvents

Various solvents, particularly polychlorinated and aromatic solvents were used for decades for extractions in synthetic organic chemistry. Some of these solvents like CCl_4 are banned and some others are restricted. Chemists use low toxic, and their waste can be recycled or decomposed at high temperatures. The chemical industry invested, under the GC principles which are less toxic to workers, and can be disintegrated more easily under normal conditions.

Design of safer chemicals and products

Many advances in method and toxicological tests bring about better understanding of the toxicity and their mechanisms of new chemicals and products. The methodology of quantitative structure-activity relationships (QSAR) can be used to speed up the evaluation of toxicity, carcinogenicity or other toxicological effects of a new chemical substance. Thanks to green chemistry (GC) principles and applications, most new chemical products have very low toxicity and are gentler to the environment. Industrial chemists have altered the synthetic way used for the making of chemical products having the following advantages as renewable raw materials, low temperature, energy savings, less waste, alternative solvents.

Developing alternative reaction conditions

Nowadays, there are numerous options or “greener” reaction techniques improving the products formation, saving energy and reducing the waste. Photochemical reactions, microwave (MW) and

ultrasound assisted organic synthetic techniques (USA OST), reactions using water as a solvent, catalytic reactions, etc. are some of the novel techniques in producing the chemicals.

Minimizing energy consumption

This is a very essential goal allowing for the energy savings and the climatic change which has become an environmental trouble. The chemical industries have spent adequate resources to reduce energy load with novelty and modify in synthetic reactions (low temperatures, reduced steps). Green chemistry (GC) is very attracted to give a research to lower energy use in each step of the manufacturing process. This was an extremely brief explanation of the mainly vital changes in future industrial processes which are going to get better effectiveness, save energy, low waste, and make safer products with less environmental impacts.

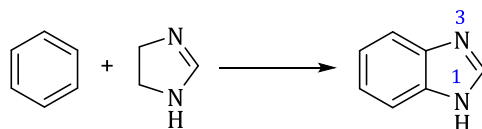
In 1990, *Anastas P.* and *Warner J.* defined green chemistry (GC): "The design of chemical products and processes that reduce or eliminate the use and generation of hazardous substances." Human society is continually facing such environmental matters and problems as ozone depletion, air pollution, global climate transform, soil and water pollution, acid rain, natural resources and an addition of hazardous waste. There are twelve principles of GC. *Anastas P.* and *Warner J.* first published GC in their book, *green chemistry: Theory and Practice*, in 1998. Both serve as members of the California green chemistry science advisory panel.

In summary, the 12 principles are:

1. Prevent waste rather than treating it or cleaning it up.
2. Incorporate all materials used in the manufacturing process in the final product.
3. Use synthetic methods that generate substances with little or no toxicity to people or the environment.
4. Design chemical products, but reduce toxicity.
5. Phase-out solvents and auxiliary substances when possible.
6. Use energy efficient processes, at ambient temperature and pressure, to reduce costs and environmental impacts.
7. Use renewable raw materials.
8. Reuse chemical intermediates and blocking agents to reduce or eliminate waste.
9. Select catalysts that carry out a single reaction many times instead of less efficient reagents.
10. Use chemicals that readily break down into innocuous substances in the environment.
11. Develop better analytical techniques for real-time monitoring to reduce hazardous substances.
12. Use chemicals with low risk for accidents, explosions, and fires.

Benzimidazole derivatives

In current years, various reports which were related to synthesis of nitrogen (N), oxygen (O) and Sulphur (S) containing heterocyclic had appeared owing to an extensive variety of their pharmacological activities. In recent years, numerous reports concerning the synthesis of heterocyclic compounds under various conditions like solvent-free, reactants immobilized on a solid support, microwave (MW) irradiation condition, green catalyst, and green solvent have appeared. Benzimidazole is a heterocyclic aromatic organic compound. It is a pharmacophore and a privileged structure in medicinal chemistry. This compound which is bicyclic consists of the fusion of benzene (**1**) and imidazole (**2**) also known as benzimidazole (**3**) (Scheme 1).



Scheme 1. Formation and structure of benzimidazole

The use of benzimidazole dates several years back and plays a very vital role with plethora of useful therapeutic activities [11], like antiulcer [12], antihypertensive [13], analgesic [14], anti-inflammatory [15], antiviral [16,17], antifungals [18], anticancer [19-23], antibacterial [24-25] and anthelmintic [26], and other biological activities. Various benzimidazole moiety congaing drugs were showing various pharmacological activities of benzimidazole (Figure 1).

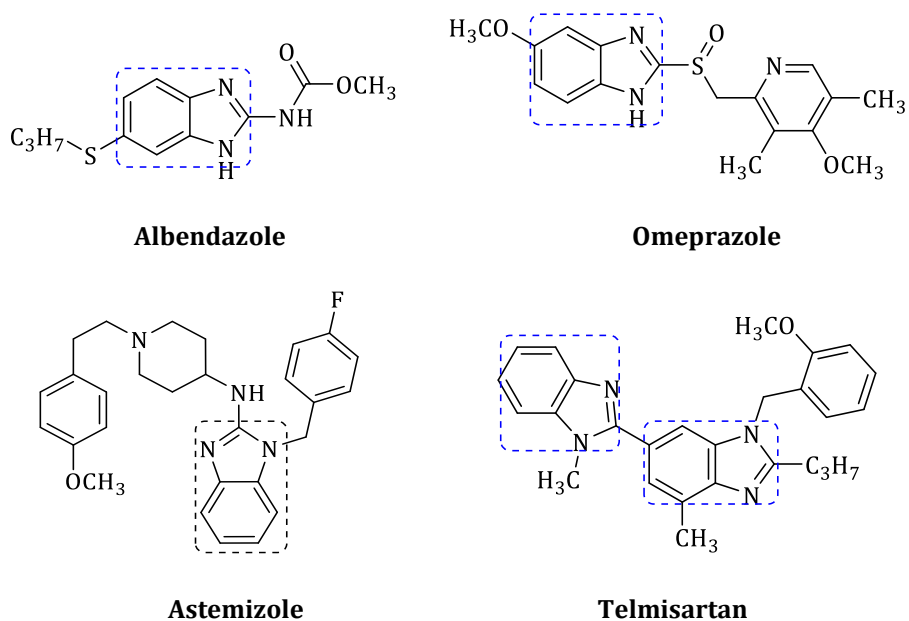
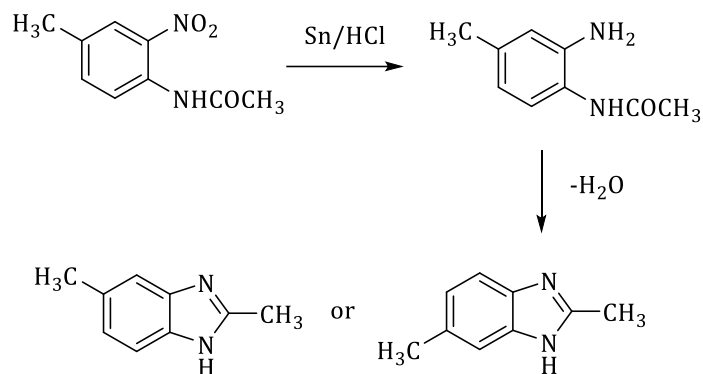


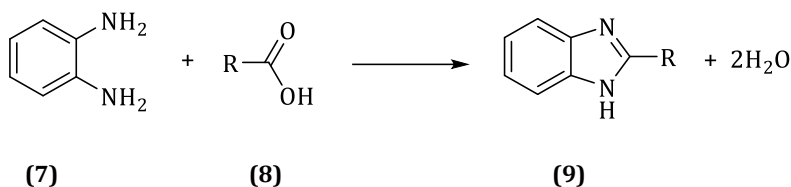
Figure 1. Some currently used drugs containing benzimidazole nucleus

The most well-known benzimidazole compound in nature is *N*-ribosyl-dimethyl benzimidazole, which provides an axial ligand for cobalt in vitamin 12 [27-29]. Historically, the first benzimidazole was prepared in 1872 by Hoebrecker, by the reduction of 2-nitro-4-methyl acetanilide (**4**) gave 2,5-dimethyl benzimidazole (**5**) or 2,6-dimethyl benzimidazole (**6**) [30-31].



Scheme 2. Synthesis of benzimidazole from 2-nitro-4-methyl acetanilide

Synthesis of benzimidazoles virtually starts with benzene derivatives having nitrogen-containing functions ortho to each other like *o*-phenylenediamines (**7**) (OPD) and reacting with different carboxylic acids (**8**) to give 2-substituted benzimidazole derivatives (**9**), generally in good yield. The reaction is carried out by heating the reactants collectively on a steam bath, or being heated under reflux or at an elevated temperature, or in a sealed tube [32].



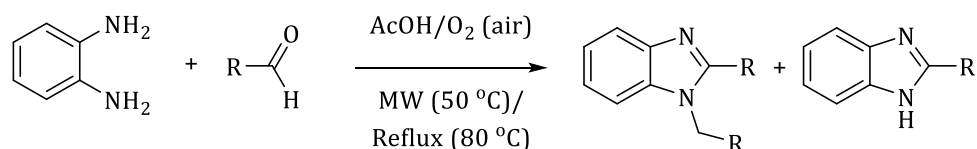
Scheme 3. The general synthetic method of synthesis of benzimidazole

In the last two decades, it has become gradually popular that the chemical and allied industries, like pharmaceuticals, are faced with troubles. Various classical synthetic methods have a broad scope but produce amounts of waste, and the chemical industry has subject to rising pressure to minimize or, eliminate these wastes. For every kg of phloroglucinol formed 40 of solid waste, having chromium sulfate $\text{Cr}_2(\text{SO}_4)_3$, ammonium chloride NH_4Cl , ferrous chloride FeCl_2 , and potassium hydrogen sulfate KHSO_4 were created and led to the preface of the environmental factor (E factor) in kilograms of wastes/kilogram of products, as a measure of the footprint of manufacturing processes in various sections of the chemical industries [33]. The E factor symbolized the actual

amount of waste produced in the procedure, defined as the whole thing and the desired products. It takes the chemical yield into account and includes reagents, solvent losses; process aids, and, in principle, even fuels. Water was usually expelled from the E factor as the addition of all process water could lead to remarkably high E factors in several cases and made assessments of processes complicated. A higher E factor means more waste and, thus, a larger environmental footprint. The ideal E factor is zero. Put relatively; it is the total mass of raw materials minus the total mass of the product, all divided by the total mass of the product. The factor of any chemical process can be minimized by relating the greener chemical methods [34].

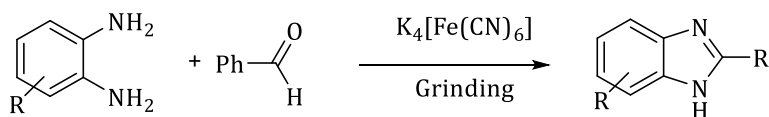
Green synthesis of benzimidazole

Synthesized benzimidazoles by condensation of *o*-phenylene diamine promoted by acetic acid under microwave (MW). They concluded that a gentle manipulated method, eco-friendly and green aspects avoiding hazardous solvents, shorter reaction times and high yields of the products are the advantages of this method [35].



Scheme 4. Microwave assisted: benzimidazole synthesis from OPD

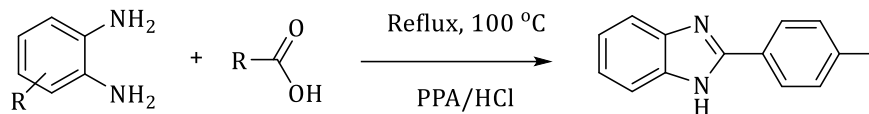
Efficiently, synthesized benzimidazoles in high yields by treatment of 1,2-diamine with aldehydes used the metal complex $K_4[Fe(CN)_6]$ as a catalyst. The method was carried out under solvent-free condition *via* oxidation of carbon-nitrogen bond which is a green, mild and inexpensive method [36].



Scheme 5. Solvent-free synthesis of benzimidazole from OPD

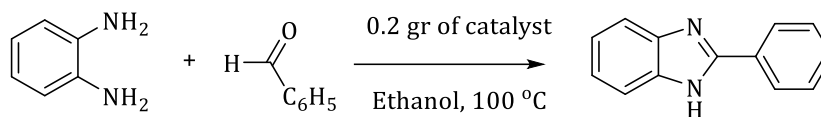
We have synthesized a set of 2-substituted benzimidazoles by condensation of phenylenediamine (OPD) with the substituted acids in the presence of ring-closing agents like polyphosphoric

acid/HCl confirming the use of a simple condensation method and ring-closing agents for the synthesis of 2-substituted benzimidazoles [37].



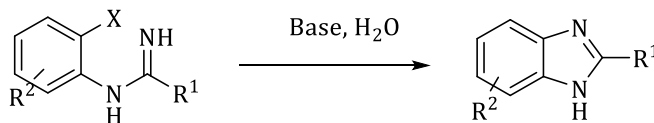
Scheme 6. Synthesis of benzimidazole from OPD, by ring closing agents

The catalytic activity of alumina, zirconia, manganese oxide/alumina, and manganese oxide/zirconia in the condensation reaction between OPD and an aldehyde or ketone to synthesize 2-substituted benzimidazoles and 1,5-disubstituted benzodiazepines [38].



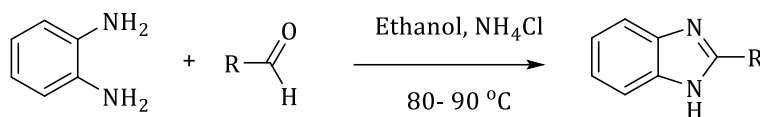
Scheme 7. Synthesis of benzimidazole from OPD in the presence of a green catalyst

A method for the synthesis of the benzimidazole ring system through a carbon-nitrogen cross-coupling reaction in the presence of K_2CO_3 in water at 100 °C for 30 h was presented. The intermolecular cyclization of *N*-(2-iodoaryl)benzamide provides benzimidazole derivatives in moderate to high yields. Surprisingly, the procedure occurs exclusively in water and doesn't require the use of any additional reagent/catalyst, rendering the method highly valuable from both environmental and economic points of view [39].



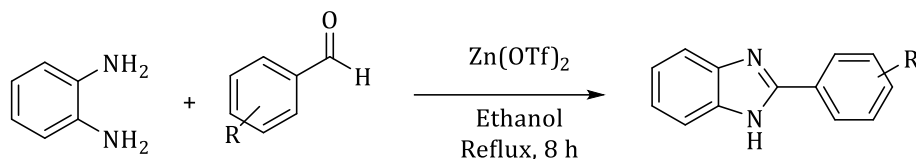
Scheme 8. Solvent/reagent-free synthesis of benzimidazole from *N*-(2-haloaryl) benzamide

We synthesized various 2-substituted benzimidazole in moderate to good yields in a one-pot reaction by condensation of OPD and an aldehyde in the presence of ammonium chloride as a catalyst at 80 to 90 °C and concluded that this method was a green and economical [40].



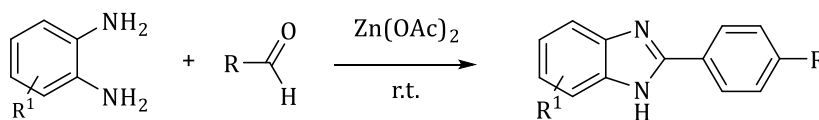
Scheme 9. Synthesis of benzimidazole from OPD by using green-catalyst

They are synthesized of benzimidazole derivatives using zinc triflate as an efficient catalyst in one-pot synthesis of 2-substituted benzimidazole derivatives from OPD and substituted aldehydes in ethanol solvent at reflux temperature. The Zinc triflate was an efficient catalyst for the formation of benzimidazole from aldehydes and OPD. It is an easily available catalyst for this protocol as being economically attractive. The simple workup procedure, high yields of products and nontoxic nature of the catalyst are other advantages of the present method [41].



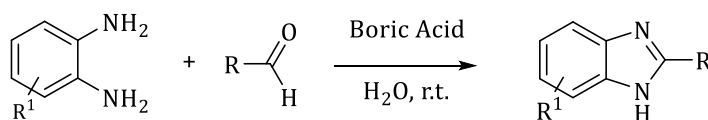
Scheme 10. Synthesis of benzimidazole from OPD by using an efficient green catalyst

Benzimidazoles derivatives are synthesized by reacting the substituted OPD with aldehyde derivatives using a catalytic amount of zinc acetate at room temperature with excellent yields. The notable selectivity under mild, neutral and solvent-free conditions, commercially available inexpensive catalyst is an attractive feature of this method [42].



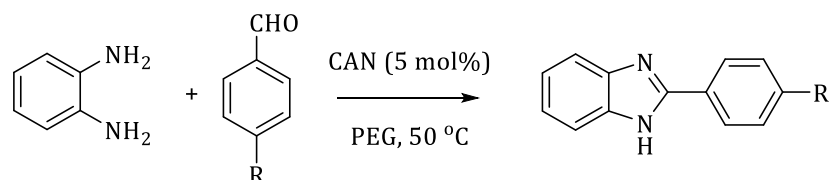
Scheme 11. Synthesis of benzimidazole from OPD by using an efficient green catalyst

It is the synthesized 2-substituted benzimidazole derivatives by one-pot reaction of OPD and aldehydes in the presence of aqueous boric acid solution at room temperature. The method was proved as convenient and the products were isolated with good yields [43].



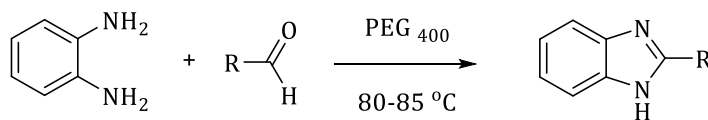
Scheme 12. Synthesis of benzimidazole from OPD by using an efficient green catalyst

It is the synthesized benzimidazole derivatives from OPD and aldehydes in PEG as a solvent with ceric ammonium nitrate (CAN) as the catalyst. This method provides a novel route for the synthesis of benzimidazoles in good yields with little catalyst loading. The recovery and the successful utilization of the solvent, furthermore, the easy set-up and purification tasks of this sustainable method make it appealing for bulk industry applications [44].



Scheme 13. Synthesis of benzimidazole from OPD by using green catalyst and green solvent

It is the synthesized benzimidazole by reacting OPD with several aldehydes using a green solvent PEG400 and got good yields [45].



Scheme 14. Synthesis of benzimidazole from OPD by using efficient green solvent

Conclusions

Green chemistry (GC) involves the use of a set of principles that reduces or removes the use or formation of hazardous substances in the design, manufacture, and application of chemical products [46]. As we design new chemical synthesis, decisions about what hazardous substances are used and what toxic materials should be handled are being made. One must consider whether hazardous waste will require extraordinary disposal, or the overall environmental issues connected to these processes. Benzimidazoles are used in many fields and are very vital for human kind, and they can also be considered as the most important nuclei in many drugs. In the conventional method of synthesis, the yield was less and the chances of environmental pollution were more, but the greener methods reduced the by-products. Even though green methods are available for the synthesis of benzimidazoles, there is a necessity for the development of further and more effective methods as the utilizations of benzimidazole derivatives not only in the field of pharmacy but also in other polymer industries.

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