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Green Synthesis of Benzimidazole Derivatives: An Overview of Bulk Drug Synthesis

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Abstract: 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. In recent decades, 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 review I tried to compile the chemistry of different derivative of substituted benzimidazole and some of the important methodologies used for the synthesis. 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 ecofriendly and economical.
Key Words: Benzimidazole, bulk synthesis, green synthesis, ecofriendly.

Introduction:

Benzimidazole is a heterocyclic aromatic organic compound. It is an important pharmacophore and a privileged structure in medicinal chemistry. This compound is bicyclic in nature which consists of the fusion of benzene (1) and imidazole (2). The numbering system for the benzimidazole (3) is as follows:

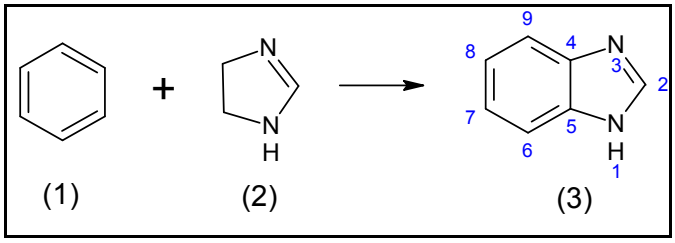

Fig 2: Structure of Benzimidazole

The use of benzimidazole dates many years back[1]. It plays a very important role with plenty of useful therapeutic activities such as:

Antiulcer[2], antihypertensive[3], analgesic[4], anti-inflammatory[5], anti-viral[6,7], antifungals[8], anticancer[9,10,11,12,13], antibacterial[14,15] and anthelmintic[16].

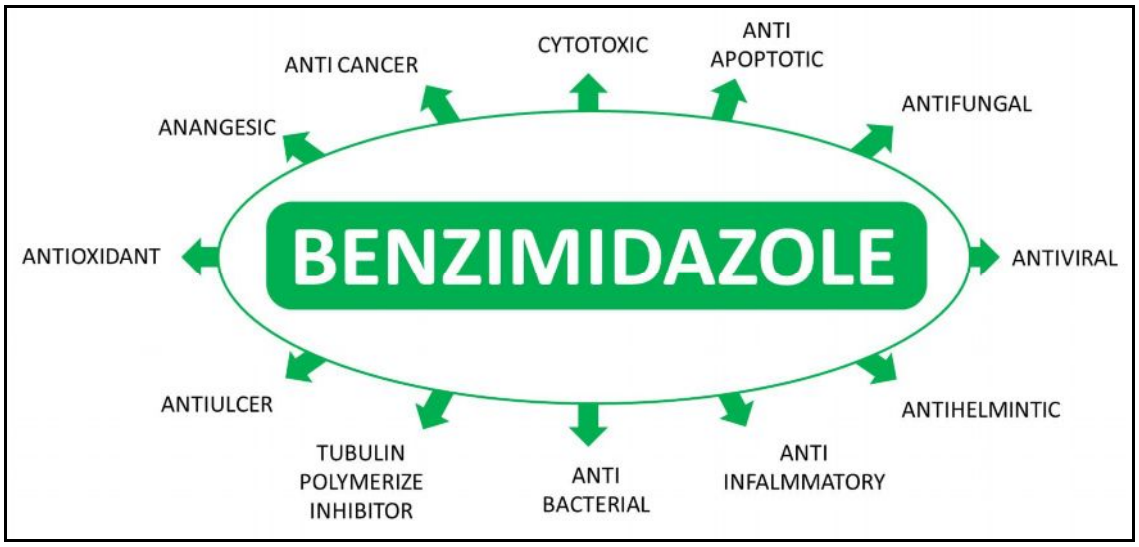

Fig.No:1 – Figure showing various pharmacological activities of Benzimidazole.

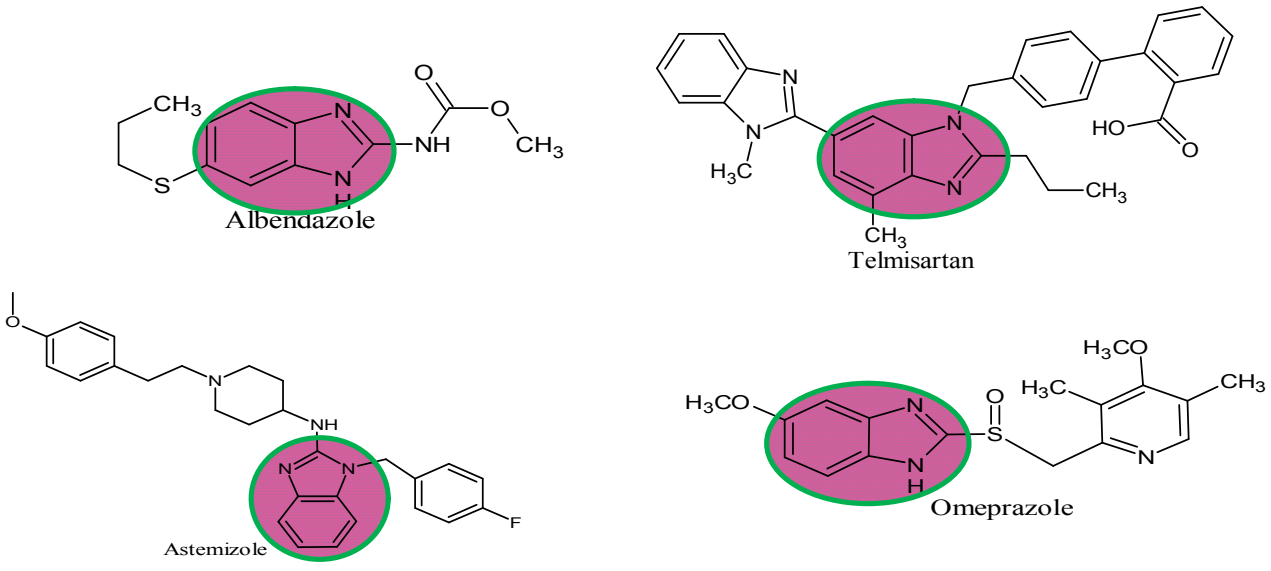

Fig 2: Some drugs containing benzimidazole as nucleus

The most prominent benzimidazole compound in nature is N-ribosyl-dimethyl benzimidazole, which serve as an axial ligand for cobalt in vitamin 12 [17,18,19]. Historically, the first benzimidazole was prepared in 1872 by Hoebrecker, who obtained 2, 5 – dimethyl benzimidazole (5) or 2, 6 – dimethyl benzimidazole (6) by the reduction of 2-nitro-4- methyl acetanilide (4) [20,21].

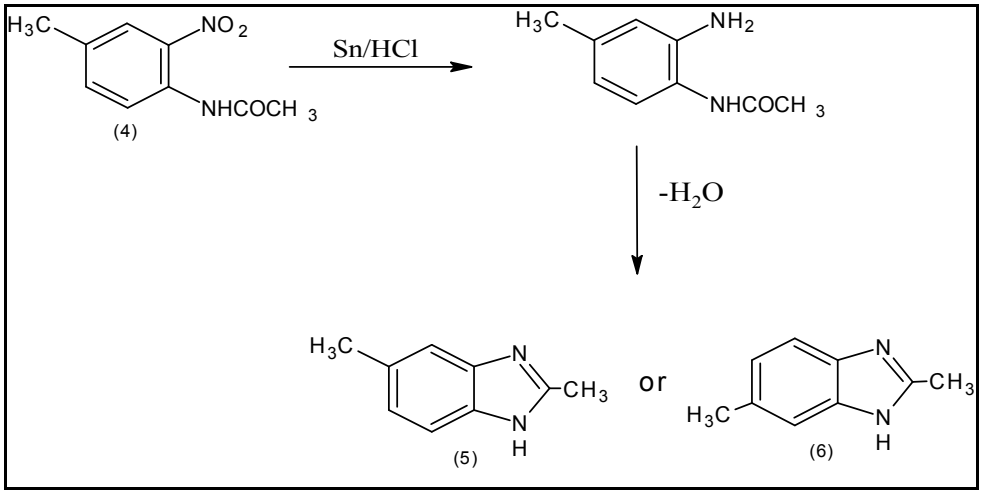

Fig 3: Synthesis of Benzimidazole from 2-nitro-4-methyl acetanilide by Hoebrecker

Preparation of benzimidazoles practically starts with benzene derivatives possessing nitrogen-containing functions ortho to each other *i.e.* the starting material o –Phenylenediamines (7) (OPD) react readily with most carboxylic acids (8) to give 2-substituted benzimidazoles (9), 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[22].

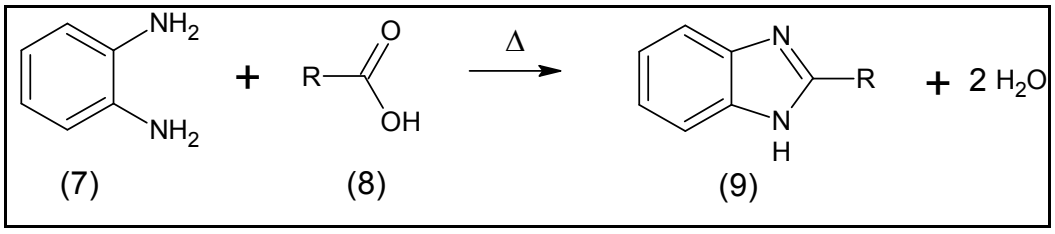

Fig 4: General Laboratory method of synthesis of benzimidazole

In the last two decades it has become increasingly clear that the chemical and allied industries, such as pharmaceuticals, are faced with serious environmental problems. Many of the classical synthetic methodologies have broad scope but generate copious amounts of waste, and the chemical industry has been subjected to increasing pressure to minimize or, preferably, eliminate this waste. For every kg of phloroglucinol produced 40 kg of solid waste, containing chromium sulphate $Cr_2(SO_4)_3$, ammonium chloride NH_4Cl, ferrous chloride $FeCl_2$ and potassium hydrogen sulphate $KHSO_4$ were generated. This led to the introduction of the **E** (environmental) **factor** (kilograms of waste per kilogram of product) as a measure of the environmental footprint of manufacturing processes[23] in various segments of the chemical industry

Table 1: E factors in the chemical industry.

Industry segment	Volume (t y^{-1}) [a)]	E factor (kg waste/kg product)
Bulk chemicals	$10^4 – 10^6$	< 1 – 5
Fine chemicals industry	$10^2 – 10^4$	5 – > 50
Pharmaceutical industry	$10 – 10^3$	25 – > 100

a - Annual production of the product world - wide or at a single site.

The E factor represents the actual amount of waste produced in the process, defined as everything but the desired product. It takes the chemical yield into account and includes reagents, solvent losses, process aids, and, in principle, even fuel. Water was generally excluded from the E factor as the inclusion of all process water could lead to exceptionally high E factors in many cases and make meaningful comparisons of processes difficult. A higher E factor means more waste and, consequently, a larger environmental footprint. The ideal E factor is zero. Put quite simply, it is the total mass of raw materials minus the total mass of product, all divided

by the total mass of product. The factor of any chemical process can be reduced or minimized by applying the greener chemical methods.

In 1990, Paul Anastas and John Warner defined Green Chemistry: *"The design of chemical products and processes that reduce or eliminate the use and generation of hazardous substances"*. Human society is constantly facing such environmental issues and problems as ozone depletion, air pollution, global climate change, soil and water pollution, acid rain, the depletion of natural resources, and the accumulation of hazardous waste. There are twelve principles of Green Chemistry. Paul T. Anastas and John C. Warner first published their 12 principles of Green Chemistry 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 to be effective, 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 for feed stocks.
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[24].

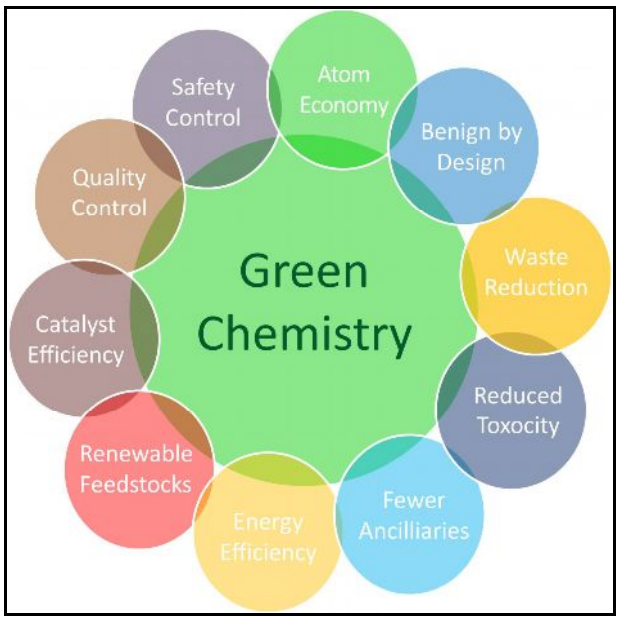

Fig 5: Principals of Green Chemistry

Green Synthesis of Benzimidazole:

Davood Azarifar et al., in 2010 Synthesised benzimidazoles by condensation of o-phyneline diamine promoted by acetic acid under microwave. They concluded that a mild, manipulatable procedure, eco-friendly and green aspects avoiding hazardous solvents, shorter reaction times and high yields of the products are the advantages of this method[25].

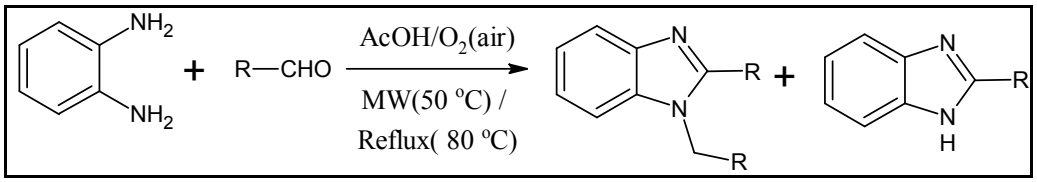

Fig 6: Microwave assisted benzimidazole synthesis from OPD by Davood A et al

Kabeer A. Shaikh et al., 2012 have been efficiently synthesized Benzimidazoles in high yields by treatment of 1, 2- diamine with aldehydes using the metal coordinate complex K4[Fe(CN)6] as a catalysis. The method was carried out under solvent free condition via oxidation of carbon-nitrogen bond which is green, mild and inexpensive process[26].

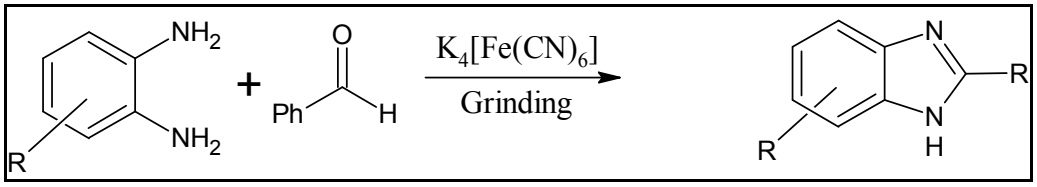

Fig 7: Solvent free synthesis of benzimidazole from OPD by Kabeer A. Shaikh et al.,

B.N.B.vaidehi et al., had synthesised set of 2-substituted benzimidazoles successfully by condensation of o-phenylenediamine with substituted acids in presence of ring closing agents like Polyphosphoric acid / HCl. The present work has demonstrated the use of a simple Cyclocondensation method, Ring closing agents for synthesis of 2-substituted benzimidazoles[27].

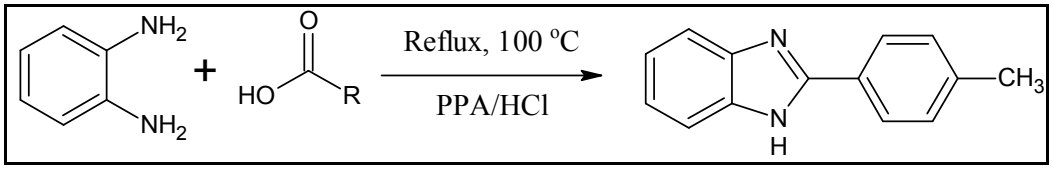

Fig 8:Synthesis of benzimidazole from OPD in presence of ring closing agents by B.N.B.vaidehi et al.,

M. Rekha et al., studied catalytic activity of alumina, zirconia, manganese oxide/alumina, and manganese oxide/zirconia in the condensation reaction between *o*-phenylenediamine and an aldehyde or a ketone to synthesise 2-substituted benzimidazoles and 1, 5-disubstituted benzodiazepines respectively and found to be simple and economical[28].

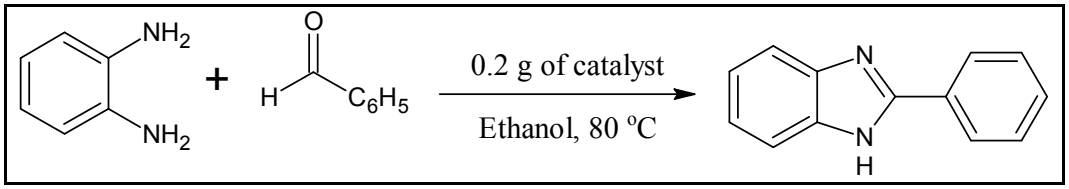

Fig 9: Synthesis of benzimidazole from OPD in presence of green catalyst

Chunxia chen et al., has been developed A straightforward method for the synthesis of the benzimidazole ring system through a carbon-nitrogen cross-coupling reaction in the presence of K2CO3 in water at 100 °C for 30 h, the intermolecular cyclization of *N*-(2-iodoaryl) benzamidine provides benzimidazole derivatives in moderate to high yields. Remarkably, the procedure occurs exclusively in water and doesn't require the use of any additional reagent/catalyst, rendering the methodology highly valuable from both environmental and economic points of view[29].

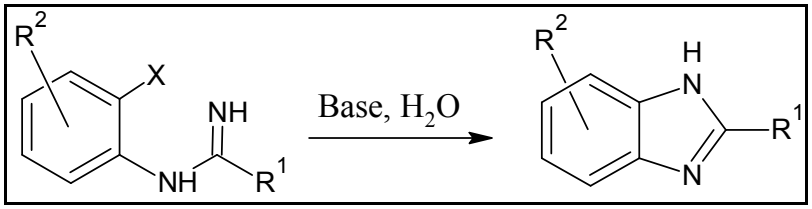

Fig 10: solvent / reagenr free synthesis of benzimidazole from *N*-(2-haloaryl) benzamidine by Chunxia chen et al.,

D Kathirvelan et al ., synthesized various 2 substituted benzimidazole in moderate to good yields in a one pot reaction by condensation of o – phynelyene diamine and an aldehyde in the presence of ammonium chloride as a catalyst at 80 to 90 ^{0}C and concluded that this method was green and economical[30].

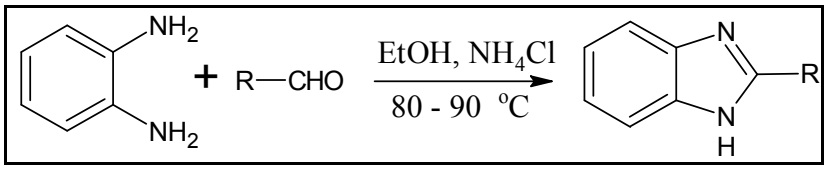

Fig 11: Synthesis of benzimidazole from OPD by using green catalyst by D Kathirvelan et al .,

Ramineni Srinivasulu et al ., synthesised of benzimidazole derivatives using zinc triflate as an efficient catalyst in one-pot synthesis of 2-substituted benzimidazole derivatives from *o*-phynelyenediamine and substituted aldehydes in ethanol solvent at reflux temperature. They concluded that Zinc triflate was found to be an efficient catalyst for the formation of benzimidazole from aldehydes and *o*-phenylenediamine. The use of this inexpensive and easily available catalyst makes this protocol practical, environment friendly and economically attractive. The simple workup procedure, high yields of products and nontoxic nature of the catalyst are other advantages of the present method[31].

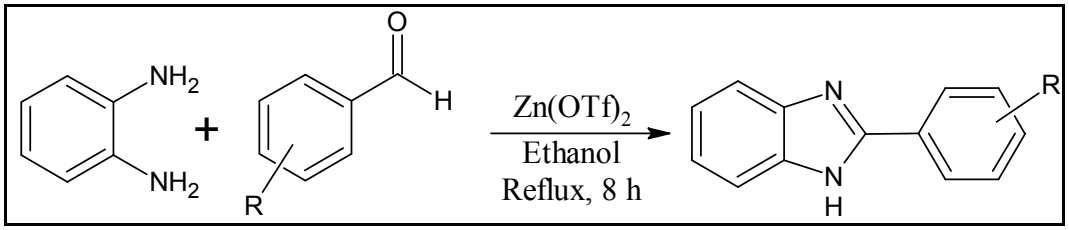

Fig 12: Synthesis of benzimidazole from OPD by using efficient green catalyst by Ramineni Srinivasulu et al .,

Vishvanath D. Patil et al., Benzimidazoles derivatives have been synthesized by reacting substituted o-phyneline diamine with aldehyde derivatives using a catalytic amount of Zinc acetate at room temperature with excellent yields. The remarkable selectivity under mild, neutral and solvent free conditions, commercially available inexpensive catalyst is an attractive feature of this method[32].

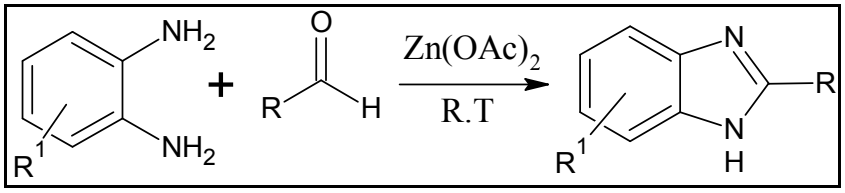

Fig 13: Synthesis of benzimidazole from OPD by using efficient green catalyst by Vishvanath D. Patil et al.,

Zahed Karimi-Jaberi et al ., had synthesised 2-Substituted in a one-pot reaction from *o*-phenylenediamine and aldehydes in the presence of boric acid in water at room temperature. The method was proved to be eco-friendly, convenient and the products were isolated with good yields[33].

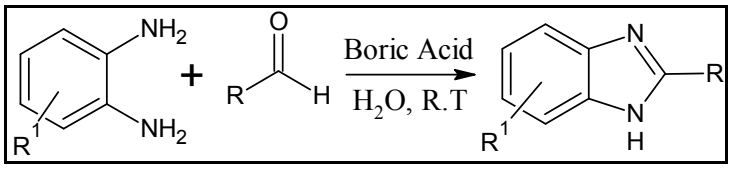

Fig 14: Synthesis of benzimidazole from OPD by using efficient green catalyst by Zahed Karimi-Jaberi et al .,

Mazaahir Kidwai et al., synthesised of benzimidazole derivatives from o-phenylenediamine and aldehydes in PEG as solvent with Ceric ammonium nitrate (CAN) as catalyst. This method provides a novel route for the synthesis of benzimidazoles in good yields with little catalyst loading. The recovery and the successful reutilization of the solvent, Moreover, the easy set-up and purification tasks of this sustainable method make it appealing for bulk industry applications[34].

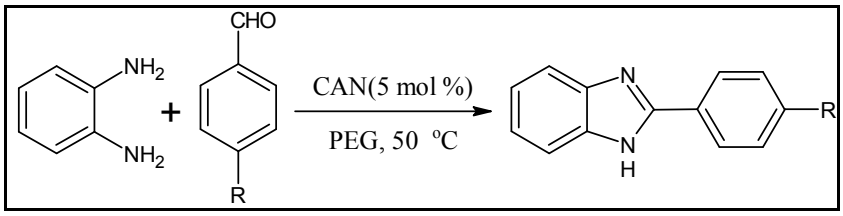

Fig 15: Synthesis of benzimidazole from OPD by using green catalyst and green solvent by Mazaahir Kidwai et al.,

Mita D. Khunt et al., has synthesised the benzimidazole by reacting o-phynelinediamine with several aldehydes using a green solvent PEG400 and got good yields[35].

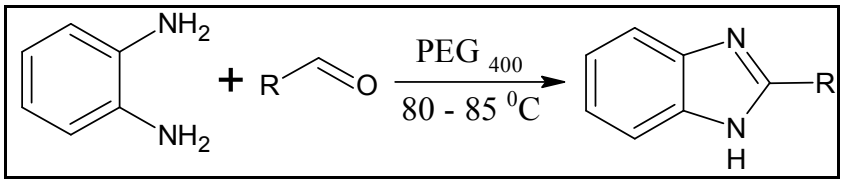

Fig 16: Synthesis of benzimidazole from OPD by using efficient green solvent by Mita D. Khunt et al.,

Conclusion:

Benzimidazoles are been used in many fields and are very essential for human kind and it is most important nuclei in many drugs. In conventional method of synthesis the yield was less and the chances of environmental pollution were more, but in greener methods the yields are higher which reduces byproducts. Even though green methods are available for the synthesis of benzimidazoles there is a necessity for the development of further more effective methods as the utilization of benzimidazole derivatives is high not only in the field of pharmacy but also in other viz polymer industry.

References:

1. Avinash Patil, Swastika Ganguly and Sanjay Surana "A Systematic Review of Benzimidazole Derivatives as an Antiulcer Agent" Rasayan, J Chem., 2008, 1(3):447-460.
2. Avinash Patil, Swastika Ganguly and Sanjay Surana , A Systematic Review Of Benzimidazole Derivatives As An Antiulcer Agent, Rasayan J. Chem Vol.1, No.3 (2008), 447-460.
3. Radhika H. Datani, Suvarna G. Kini, Muhammad Mubeen Journal of Computational Methods in Molecular Design, 2012, 2 (4):149-157.

4. Md. Hamiduzzaman, Sultana Juhara Mannan, Avijit Dey and S. M. Abdur Rahman , Evaluation of analgesic, antipyretic, hypoglycemic and CNS depressant activity of 2-bromopopylamine hydrobromide, 3-bromo popyl ammonium bromide, ortho-amino aniline and benzimidazole-2-thiol in animal model , Der Pharmacia Lettre, 2014, 6 (1):47-53.
5. Anna Pratima Nikalje, Mangesh Ghodke, One Pot Green Synthesis Of 2-Aryl/Heterylbenzimidazole As Anti Inflammatory Agents, World Journal Of Pharmacy And Pharmaceutical Sciences Volume 3, Issue 2, 1311-1322.
6. Ashish Kumar Tewari & Anil Mishra, Synthesis and antiviral activities of N-substituted-2-substituted-benzimidazole derivatives , Indian Journal of Chemistry Vol. 45B, February 2006, pp. 489-493.
7. Ting Pan, Xin He, Bing Chen, Hui Chen, Guannan Geng, Haihua Luo, Hui Zhang, Chuan Bai, Development of benzimidazole derivatives to inhibit HIV-1 replication through protecting APOBEC3G protein, European Journal of Medicinal Chemistry 95 (2015) 500-513.
8. Hament Panwar, Ranjana Dubey, Nidhi Chaudhary and Tilak Ram A green approach for the heterocyclization of 2-substituted benzimidazoles: Synthesis, characterisation and pharmacological evaluation Der Pharma Chemica, 2013, 5(6):192-200.
9. Kapuriya Kaushik, Ganure Ashok, Davda Swati, Kitawala Mustafa, Topiya Hiral, Benzimidazole: A Promising Lead For Anticancer Drug Design, Universal Journal of Pharmacy, 2013, 02 (03): Page 57-62.
10. T. Srinivasa Reddy, Hitesh Kulhari, V. Ganga Reddy, Vipul Bansal, Ahmed Kamal, Ravi Shukla, Design, synthesis and biological evaluation of 1,3-diphenyl-1Hpyrazole derivatives containing benzimidazole skeleton as potential anticancer and apoptosis inducing agents, European Journal of Medicinal Chemistry 101 (2015) 790-805.
11. . Qi Guan, Chunming Han, Daiying Zuo, Min'an Zhai, Zengqiang Li, Qian Zhang, Yanpeng Zhai, Xuewei Jiang, Kai Bao, Yingliang Wu, Weige Zhang, Synthesis and evaluation of benzimidazole carbamates bearing indole moieties for antiproliferative and antitubulin activities, European Journal of Medicinal Chemistry 87 (2014) 306-315.
12. Alka Sharma, Vijay Luxami, Kamaldeep Paul, Purine-benzimidazole hybrids: Synthesis, single crystal determination and in vitro evaluation of antitumor activities, European Journal of Medicinal Chemistry 93 (2015) 414-422.
13. Yan-Ting Wang, Ya-Juan Qin, Na Yang, Ya-Liang Zhang, Chang-Hong Liu, Hai-Liang Zhu, Synthesis, biological evaluation, and molecular docking studies of novel 1-benzene acyl-2-(1-methylindol-3-yl)-benzimidazole derivatives as potential tubulin polymerization inhibitors, European Journal of Medicinal Chemistry 99 (2015) 125-137.
14. Yeong Keng Yoon, Mohamed Ashraf Ali, Ang Chee Wei, Tan Soo Choon, Rusli Ismail, Synthesis and evaluation of antimycobacterial activity of new benzimidazole aminoesters, European Journal of Medicinal Chemistry 93 (2015) 614-624.
15. Jurupula Ramprasad, Nagabhushana Nayak, Udayakumar Dalimba a, Perumal Yogeeswari, Dharmarajan Sriram, S.K. Peethambar, Rajeshwara Achur, H. S. Santosh Kumar, Synthesis and biological evaluation of new imidazo[2,1-b][1,3,4] thiadiazole-benzimidazole derivatives, European Journal of Medicinal Chemistry 95 (2015) 49-63.
16. Srikanth Lingala, Raghunandan Nerella, K. R. S. Sambasiva Rao Synthesis, antimicrobial and anthelmintic activity of some novel benzimidazole derivatives Der Pharma Chemica, 2011, 3 (4):344-352.
17. Babita Goswami, Arvind Kumar Singh , Pharmacological activities of benzimidazole derivatives-Overview, IJSID, 2012, 2 (1), 121-136.
18. Manna K, Aggarwal Y. Microwave assisted synthesis of new indophenazine 1,3,5 - trisubstituted pyrrazoline derivatives of benzofuran and their antimicrobial activity. Bioorg. Med. Chem. Lett. 2009; 19: 2688-2692.
19. Ramanpreet Walia, Md.Hedaitullah, Syeda Farha Naaz, Khalid Iqbal and HS. Lamba, Benzimidazole derivatives-An overview, IJRPC 2011, 1(3), 565-574.
20. JB Wright. The chemistry of the benzimidazoles, 1951; 38: 397-541.
21. Uday Kalidhar, Amandeep Kaur, An Overview on Some Benzimidazole and Sulfonamide Derivatives with Anti-Microbial Activity, RJPBCS , October – December 2011, Volume 2, Issue 4 Page No. 1116.
22. B.S Furniss et al., Text book of practicle organic chemistry, 4th edition, 1162-1163.
23. Roger A. Sheldon, Atom efficiency and catalysis in organic synthesis, Pure Appl. Chem., Vol. 72, No. 7, pp. 1233–1246, 2000

24. Anastas PT, Warner JC, Green Chemistry: Theory and Practice. Oxford University Press, Oxford 1998.
25. Davood Azarifar, Mojgan Pirhayati, Behrooz Maleki, Mehrangiz Sanginabadi and Razieh Nejat Yami, Acetic acid-promoted condensation of o-phenylenediamine with aldehydes into 2-aryl-1 (arylmethyl)-1H-benzimidazoles under microwave irradiation, J. Serb. Chem. Soc. 75 (9) 1181–1189 (2010)
26. Kabeer A. Shaikh, An efficient solvent-free synthesis of imidazolines and benzimidazoles using K4[Fe(CN)6] catalysis Org. Commun. 5:1 (2012) 12-17.
27. B.N.B.Vaidehi, Synthesis And Biological Evaluation Of 2-Substituted Benzimidazoles, Int J Pharm Bio Sci 2012 July; 3(3): P 26 – 31
28. Rekha, M.; Hamza, A.; Venugopal, B.R.; Nagaraju, N. Synthesis of 2-substituted benzimidazoles and 1,5–disubstituted benzodiazepines on alumina and zirconia catalysts. Chin. J. Catal. 2012, 33,439–446.
29. Chunxia Chen, Chen Chen, Bin L, Jingwei Tao and Jinsong Peng, Aqueous Synthesis of 1-H-2-Substituted Benzimidazoles via Transition-Metal-Free Intramolecular Amination of Aryl Iodides, Molecules 2012, 17, 12506-12520.
30. D Kathirvelan, P Yuvaraj, K Babu, Arasampattu S Nagarajan & Boreddy S R Reddy, A green synthesis of benzimidazoles, Indian journal of chemistry, Vol.52B, 2013, 1152-1156.
31. Ramineni Srinivasulu, Kannasani Ravi Kumar, Peruri Veera Venkata Satyanarayana, Facile and Efficient Method for Synthesis of Benzimidazole Derivatives Catalyzed by Zinc Triflate, Green and Sustainable Chemistry, 2014, 4, 33-37.
32. Vishvanath D. Patil, Gole Medha, Mhatre Shramesha, Jaiswal Aarti, A mild and efficient synthesis of Benzimidazole by using lead peroxide under solvent free condition, Der Chemica Sinica, 2010, 1 (2): 125-129.
33. Zahed Karimi-Jaberi, Mohammad Amiri, An Efficient and Inexpensive Synthesis of 2-Substituted Benzimidazoles in Water Using Boric Acid at Room Temperature E-Journal of Chemistry 2012, 9(1), 167-170.
34. Mazaahir Kidwai, Nwar Jahan and Divya Bhatnagar, Polyethylene glycol: A recyclable solvent system for the synthesis of benzimidazole derivatives using CAN as catalyst, J. Chem. Sci., Vol. 122, No. 4, July 2010, pp. 607–612.
35. Mita D. Khunt, Vipul C. Kotadiya, Denish J. Viradiya, Bharat H. Baria and Umed C. Bhoya, Easy, Simplistic and Green Synthesis of Various Benzimidazole and Benzoxazole Derivatives Using PEG400 as a Green Solvent, International Letters of Chemistry, Physics and Astronomy Vol. 25 (2014) pp 61-68.

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