JOURNAL OF PHARMACEUTICAL SCIENCE AND BIOSCIENTIFIC RESEARCH (JPSBR)

(An International Peer Reviewed Pharmaceutical Journal that Encourages Innovation and Creativities)

Boric Acid Catalyzed Synthesis of Benzimidazoles in Aqueous Medium

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ABSTRACT:

ABSTRACT: Water mediated green reaction of aromatic aldehyde with o-phenylenediamane in order to generate benzimidazoles using boric acid as a catalyst in water at room temperature furnished benzimidazoles in good yields. This protocol corresponds in short reaction time, low cost, high reaction yield

KEYWORDS: Aromatic aldehyde, o-phenylenediamane , Benzimidazoles ,Boric acid

Article history:

Received 01 Nov 2015
Revised 14 Nov 2015
Accepted 16 Nov 2015
Available online 15 Oct 2015

Citation:

Rajale T., Patil D. D. Boric Acid Catalyzed Synthesis of Benzimidazoles in Aqueous Medium. **J Pharm Sci Bioscientific Res**. 2015. 5(5):479-786

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INTRODUCTION:

Concept of Green Chemistry

Green chemistry is the utilization of a set of principles that will help reduce the use and generation of hazardous substances during the manufacture and application of chemical products. Green chemistry aims to protect the environment not by cleaning up, but by inventing new chemical processes that do not pollute. It is a rapidly developing and an important area in the chemical sciences.

Importance of Green Chemistry

- Waste Minimization at Source
- Use of Catalysts in place of Reagents
- Using Non-Toxic Reagents
- Use of Renewable Resources
- Improved Atom Efficiency
- Use of Solvent Free or Recyclable Environmentally Benign Solvent Systems.

Why Do We Need Green Chemistry?

- Chemistry is undeniably a very prominent part of our daily lives.
- Chemical developments also bring new environmental problems and harmful unexpected side effects, which result in the need for 'greener' chemical products.
- A famous example is the pesticide DDT.

- Green chemistry looks at pollution prevention on the molecular scale and is an extremely important area of Chemistry due to the importance of Chemistry in our world today and the implications it can show on our environment.
- The Green Chemistry program supports the invention of more environmentally friendly chemical processes which reduce or even eliminate the generation of hazardous substances.
- This program works very closely with the twelve principles of Green Chemistry.

Principles of Green Chemistry

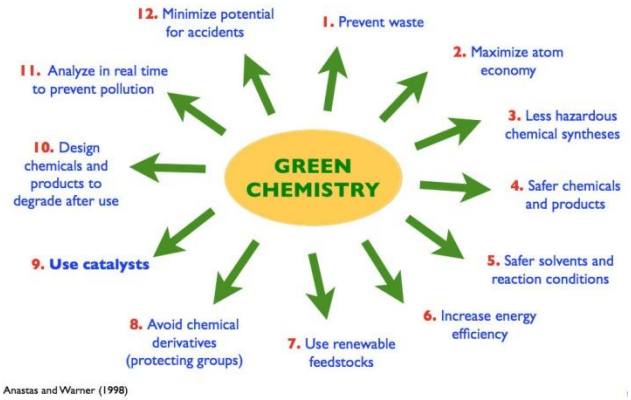


Figure 1 Principles of green chemistry

1. **Maximize atom economy:** Design syntheses so that the final product contains the maximum proportion of the starting materials. There should be few, if any, wasted atoms.

2. **Use safer solvents and reaction conditions:** Avoid using solvents, separation agents, or other auxiliary chemicals. If these chemicals are necessary, use innocuous chemicals.

3. **Increase energy efficiency:** Run chemical reactions at ambient temperature and pressure whenever possible.

4. **Design chemicals and products to degrade after use:** Design chemical products to break down to innocuous substances after use so that they do not accumulate in the environment.

5. **Analyze in real time to prevent pollution:** Include in-process real-time monitoring and control during syntheses to minimize or eliminate the formation of byproducts.

6. **Minimize the potential for accidents:** Design chemicals and their forms (solid, liquid, or gas) to minimize the potential for chemical accidents including explosions, fires, and releases to the environment.

7. **Prevent waste:** Design chemical syntheses to prevent waste, leaving no waste to treat or clean up.

8. **Design safer chemicals and products:** Design chemical products to be fully effective, yet have little or no toxicity.

9. **Design less hazardous chemical syntheses:** Design syntheses to use and generate substances with little or no toxicity to humans and the environment.

10. **Use renewable feedstocks:** Use raw materials and feedstocks that are renewable rather than depleting. Renewable feedstocks are often made from agricultural products or are the wastes of other processes; depleting feedstocks are made from fossil fuels (petroleum, natural gas, or coal) or are mined.

11. **Use catalysts, not stoichiometric reagents:** Minimize waste by using catalytic reactions. Catalysts are used in small amounts and can carry out a single reaction many times. They are preferable to stoichiometric reagents, which are used in excess and work only once.

12. **Avoid chemical derivatives:** Avoid using blocking or protecting groups or any temporary modifications if possible. Derivatives use additional reagents and generate waste.

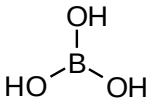
<u>Importance of Catalyst</u>

- Catalyst increases the rate of a reaction by helping break chemical bonds in reactant molecules.
- This effectively means the activation energy is reduced.
- Therefore at the same temperature, more reactant molecules have enough kinetic energy to react compared to the unanalyzed situation and so the reaction speeds up with the greater chance of a “fruitful “collision.
- Although a true catalyst does take part in the reaction, it does not get used up and can be reused with more reactants; it may change chemically on a

temporary basis but would be reformed as the reaction products also form.

- However a solid catalyst might change physically permanently by becoming more finely divided, especially if the reaction is exothermic.

Importance of boric acid as catalyst



structure of boric acid

- Boric Acids (H_3BO_3) are theoretically composed of boric oxide and water. Crystalline in composition, white in appearance, they can be used as granules or as a powder. Both forms are stable under normal conditions, free-flowing, and easily handled by means of air or mechanical conveying. In solution, they are mildly acidic.

- Boric acids are a stable crystalline product that does not change chemically under normal storage conditions.

- The development of rapid, simple, efficient, clean, high yielding, environmentally benign protocol using new catalyst for the synthesis of benzimidazoles and its derivatives are desirable.

- Boric acid is a water soluble inexpensive, stable, readily available, easy to handle catalyst and has been found effective in various transformations such as synthesis of aza Michael[1], thia Michael[2], transesterification of ethylacetoacetate[3], synthesis of α-hydroxyamides[4], bromination, oxidation of sulphides[5], beginelli reaction[6], 1,5- benzodiazepine derivatives[7], 2-amino,3-5 dicarbonitrile-6-thio-pyridene[8]. It is therefore important to examine the behavior of boric acid as a catalyst in the synthesis of benzimidazoles and its derivatives.

Importance of Benzimidazoles

- Benzimidazoles are an important group of heterocyclic compounds that are biologically active & of significant importance in medicinal chemistry. Benzimidazole is a bicyclic compound having imidazole ring, containing two Nitrogen atom at adjacent position fused to benzene ring. The benzimidazole ring is an important pharmacophore in modern drug discovery.

- A variety of benzimidazole is in use, like thiabendazole & flubendazole (anthelmintic), omeprazole & lansoprazole (antiulcerative) & astemizole (antihistaminic) . In light of the affinity, they display towards a variety of enzymes & protein receptors, medicinal chemists would certainly classify them as privileged 'sub-structures' for drug dosing. The chemistry & pharmacology of benzimidazoles have been of great intrest to medicinal chemistry because its derivatives possessed various biological activities such as antioxidant[9], antimicrobial[10], anthelmintic[11], anticancer[12], antihypertensive[13],antineoplastic, anti-inflammatory[14], analgesic[15], antiprotozoa[16]l, anti-hepatities B virus[17], antiulcer[18], antiviral[19], antifungal[20], & anticonvulsant[21], activity.

- Almost all benzimidazole derivatives with their two ring systems bear different functional substituents & this leads to essential modification of the physic-chemical, metabolic & pharmacokinetic properties of these drugs. In the past few decades, benzimidazole & its derivatives have received much attention due to their chemotherapeutic values.

Microbial Activities of Benzimidazoles

- Benzimidazole shows their antibacterial activity by inhibiting the bacterial nucleic acid & protein synthesis. This ability of beenzimidazole is due to their structural similarities with the purine[22]. 2-substituted benzimidazole derivatives are found to be pharmacologically more potent & hence the design & synthesis of 2-substituted benzimidazoles are the potential area of research[23].2-{2-(5-phenyl-1H-tetrazol-1-yl)phenyl}-1H-benzo[d]imidazole (Fig.I) were synthesized & their antimicrobial activity were tested against Gram positive *Staphylococcus aureus* & Gram negative *Escherichia coli*. The result indicated that compound were more active against the microorganisms.

- Recent study has indicated that some benzimidazole derivatives could exhibit potent anti-HBV activity with very low cytotoxicity. A series of 2-arylbenzimidazole (Fig.II)derivatives were synthesized which show inhibitory activity against *Flevivirus, Pestivirus,*

Reteroviridae, Piconiviridae, Reoviridae, Herpesveridae & Poxviridae[24].

- Benzimidazole carbamates are useful for the treatment of *Giardia lamblia; Cryptococcus neoformans, Trichomonas vaginalis, Pneumocystis carinii & Encephalitozoon intestinalis.* Therefore some new methyl benzimidazole carbamate derivatives having 5(6)-fluoro-6(5)-substituted heterocyclic rings (Fig.III) have been synthesize & their antifungal activities were investigated against *C.albicans*[25].

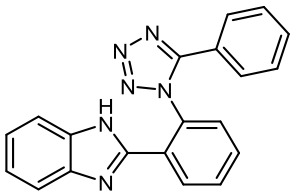


Fig. I

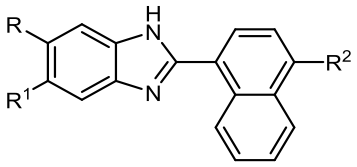


Fig. II

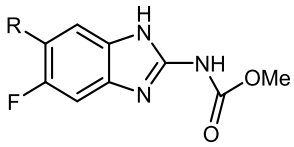
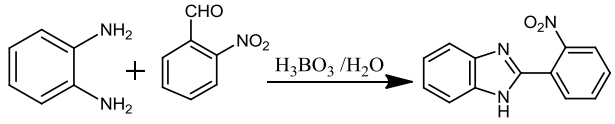


Fig. III

Result & Discussion

- In organic synthesis here we are pleased to report that a mixture of aldehyde, o-phenylenediamane in presence of boric acid (10 mol %) in water at room temperature furnished benzimidazoles in good yields (Scheme 1)



Scheme 1

Table 1:- Model reaction of o-phenylenediamine (0.01 mol) with 2-nitrobenzaldeyde (0.01 mol) by using different amounts of catalyst boric acid in water at room temperature.

Entry	Amount of catalyst (%)	Reaction time (min)	Yield (%)
1	0	50	0
2	5	50	55
3	10	25	90
4	15	80	85
5	20	80	80

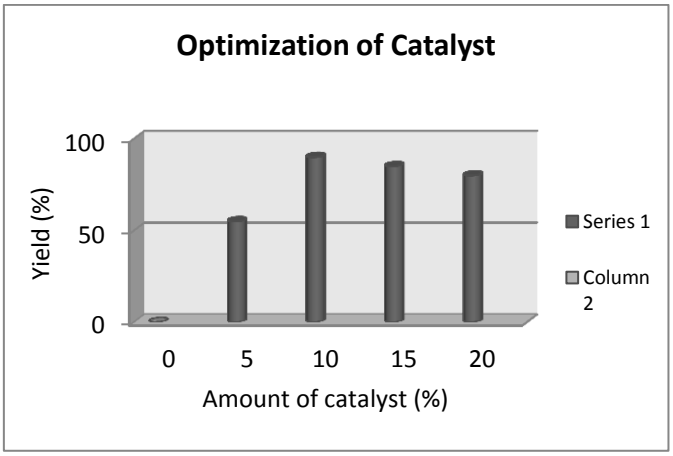
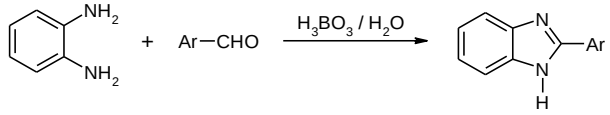


Figure: 2 Optimization of Catalyst

- The reaction was optimized by varying amount of catalyst. We chose the reaction between o-phenylenediamine 1 & 2-nitrobenzaldehyde 2a as the model reaction. First we carried out model reaction in presence of a catalyst (Table 1, entry 1) & found that the reaction did not proceed. Next, the amount of catalyst was varied with respect to 1 (Table 1, entries 2-5). It was found that only 55% & 85% yields were obtained by taking 5% & 20% amounts of catalyst boric acid (Table 1, entries 2&5), respectively. The best result (90% yield of product 3a).was obtained by using 10% amount of catalyst (Table 1, entry 3). By using these optimized conditions, various benzimidazole derivative 3a-h were synthesized in shorter time as well as in high yields using boric acid as the catalyst.

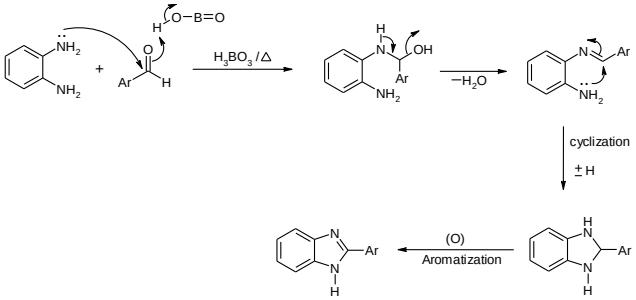
- A wide range of aromatic aldehydes were subjected to prove the general applicability of our present procedure which is summarized in Table 2. It was observed that the aromatic aldehyde bearing an electron withdrawing substituent underwent the conversion smoothly as compared to that bearing an electron donating substituent & required less time to synthesis (Table 2). We have synthesized compounds 3a-h bearing an electron withdrawing substituent (-NO_2) 3a in 30 min with high yields were as compounds 3g bearing an electron donating substituent (-OH) in 80 min.

Reaction



Scheme 1.

Reaction mechanism



Experimental Section

Procedure for Synthesis of 2-(2-Nitrophenyl)-1-H-benzo [d] imidazole (3a)

- A mixture of o-phenylenediamine (1.08gm, 0.01 mol), 2-nitrobenzaldehyde (1.51gm, 0.01 mol),& boricacid (10 mole%) in water (20 ml) was stirred at room temperature for 25 min. After completion of reaction , as monitored by TLC (ethyl acetate / n-hexane,1:5) the solid product was isolated in ice cold water & collected by simple filtration & washed with water. The crude product (3a) was purified by recrystallisation from ethanol.

Spectral analysis

IR SPECTRUM

- **2-(3-Chlrophenyl)-1H-benzo[d]imidazole**

Yellow powder; M.P:242^{o}C; IR:υ in $cm^{-1:}$ 733.782,675.928,1076.08, 1438.64, 3562.84. ^{1}H NMR: δ in ppm: 4.20(1H,NH),7.45-7.6o(m,2H),7.82-7.95(d,2H) 8.75-8.50(m,2H). EIMS:m/z (%): 228 (m*100),194(5).

Table 2:- Synthesis of Benzimidazole 3a-h by using boric acid in water.

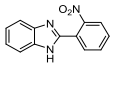
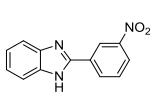
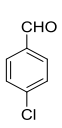
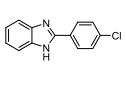
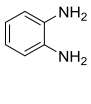
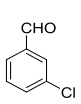
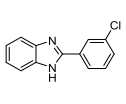
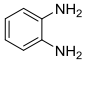
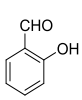
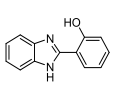
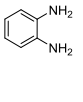
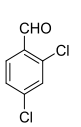
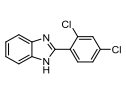
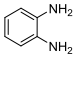
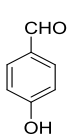
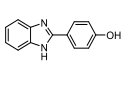
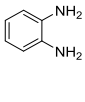
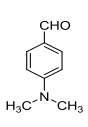
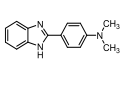
Entry	Diamine	Aldehydes	Name of Products	Time (min)	Yield (%)	Melting Point(^{o}C)
3 a				25	90	248-250
3 b				35	88	210-212
3 c				55	85	285-287
3 d				45	65	241-243
3 e				70	92	237-240
3 f				35	86	224-227
3 g				70	88	278-280
3 h				80	87	203-206

Table 3:- Reaction of o-phenylenediamine with o-nitrobenzaldehyde using different solvents.

Entry	Solvent	Time(min)	Yield(%)
1	Water	25	90
2	Ethanol	40	80
3	Methanol	65	60
4	DMF	80	60
5	DMSO	95	64
6	Acetonitrile	105	44

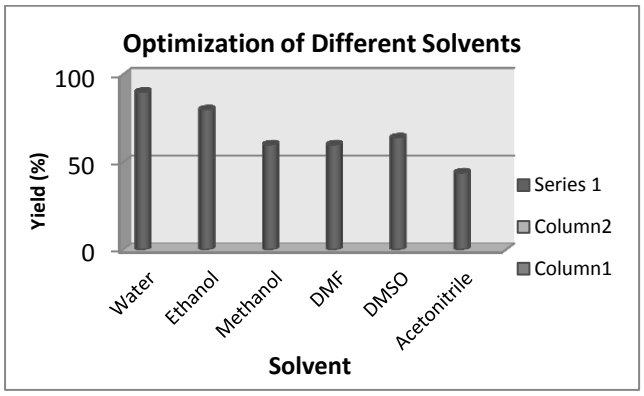


Figure 3 Optimization of different solvent

- The NMR and mass spectra are represented in fig.IV.
- The IR spectrum is represented in fig.V
- **2-(2-Nitrophenyl)-1H-benzo[d]imidazole**
- Red powder; M.P:249^{0}C; IR: υ in cm^{-1}:1336.43,1516.74,3444.24,1136.83, 740.531. ^{1}H NMR: : δ in ppm: 7.10-7.15(m,2H),7.30(d,2H),7.35(d,1H),7.45(t,1H),8.0(d,2H). EIMS:m/z (%): 240 (m*100),226(5),211(10),194(20),182(5).
- The NMR and mass spectra are represented in fig.VI.
- The IR spectrum is represented in fig.VII.

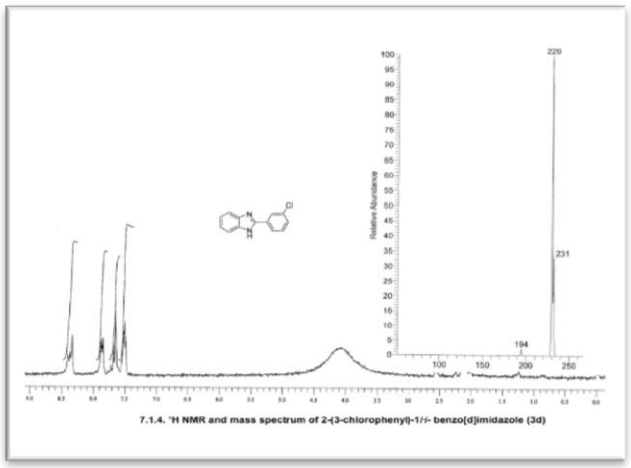


Figure 4 NMR and mass spectra of 2-(3-Chlrophenyl)-1H-benzo[d]imidazole

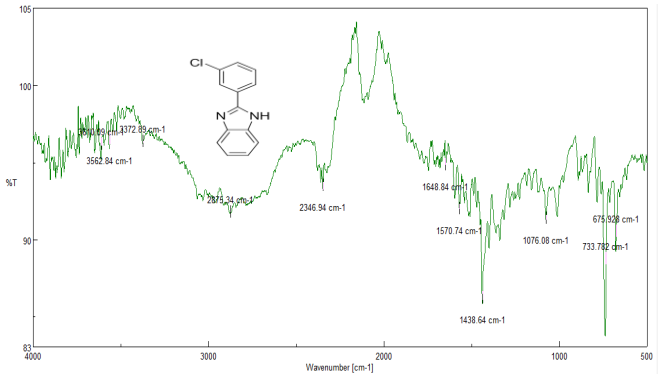


Figure 5 IR spectrum of 2-(3-Chlrophenyl)-1H-benzo[d]imidazole

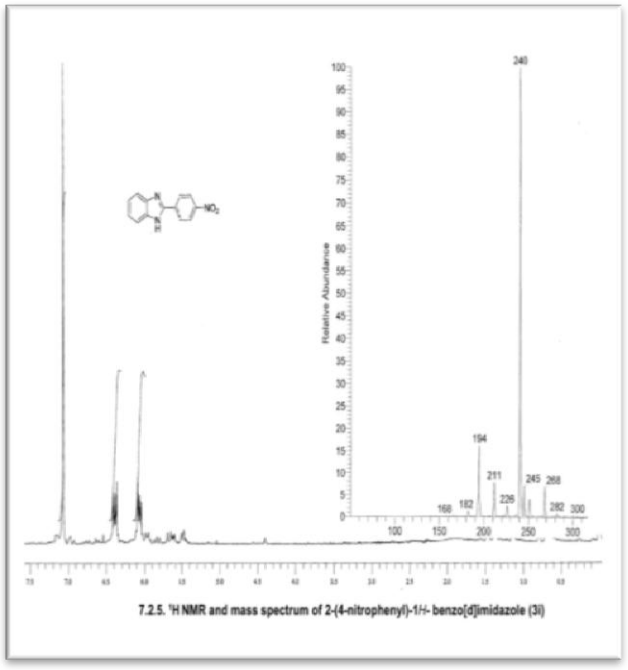


Figure 6 NMR and mass spectra of 2-(2-Nitrophenyl)-1H-benzo[d]imidazole

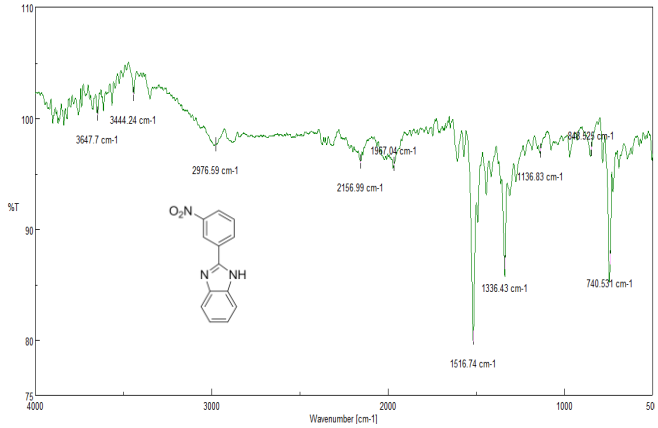


Figure 7 IR spectrum of 2-(2-Nitrophenyl)-1H-benzo[d]imidazole

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