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MICROWAVE ASSISTED SYNTHESIS OF BENZIMIDAZOLE AND ITS CHARACTERIZATION

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1. INTRODUCTION

Microwave technology opens up new opportunities to the synthetic chemist in the form of new reactions that are not possible using conventional heating. The interest in the microwave assisted organic synthesis has been growing during the recent years.[1-2]

The short reaction times provided by microwave synthesis make it ideal for rapid reaction scouting and optimization of reaction conditions, allowing very rapid progress through the hypotheses–experiment–results iterations, i.e. finding the optimum conditions for a specific reaction to obtain the desired products in good yields and purities. Since many synthesis reactions require at least one or more heating steps for long time periods, these optimizations are often difficult and time- consuming.[3]

Microwave-assisted heating under controlled conditions has been shown to be a valuable technology for any application that requires heating of a reaction mixture, since it often dramatically reduces reaction times – typically from days or hours to minutes or even seconds. Compounds can therefore be rapidly synthesized in either a parallel or (automated) sequential way using this new promising technology.[4]

Microwave-assisted organic synthesis has revolutionized organic synthesis. Small molecules can be built in a fraction of the time required by classical thermal methods. As a result, this technique has rapidly gained acceptance as a valuable tool for accelerating drug discovery and development processes.[5]

Microwave (MW) irradiation, an unconventional energy source, has been used for a variety of applications including organic synthesis, wherein chemical reactions are accelerated because of selective absorption of MW energy by polar molecules.[6]

The microwave assisted reactions occur more rapidly, safely and with higher chemical yields.[8]

Microwave-assisted organic synthesis (MAOS) is now entering the new technologies area as a tour de force in process, medicinal and combinatorial chemistry. We hope to demonstrate in this review the utility of this technique, and the potential that this methodology can give to the bench chemist.[9]

The chief features of the microwave reactions are the enhanced selectivity, much improved reaction rates, milder reaction conditions and formation of cleaner products.[10]

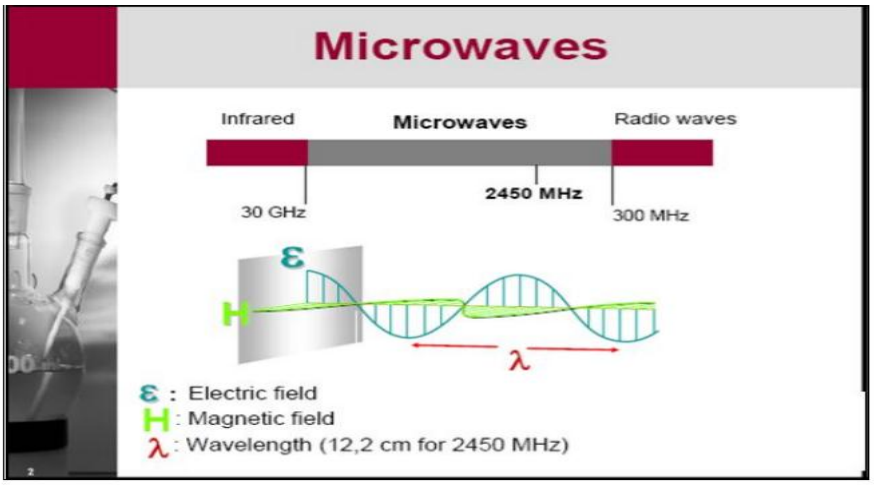
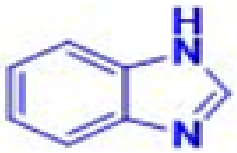


Fig. 1 :- Principle of microwave.

2. Benzimidazole



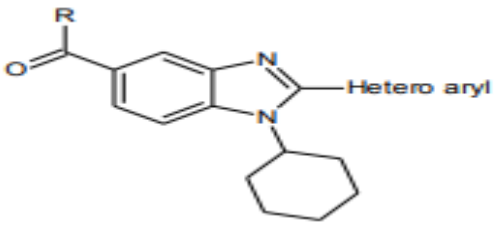
Benzimidazole is a heterocyclic aromatic organic compound. Benzimidazole moieties are a very important class of heterocyclic compounds that have many applications in pharmaceutical chemistry. This compound is bicyclic in nature which consists of the fusion of benzene and imidazole. Nowadays is a moiety of choice which possesses many

pharmacological properties. The most prominent benzimidazole compound which serves as an axial ligand for cobalt in vitamin B12 in nature is N-ribosyl-dimethylbenzimidazole.[11]

Benzimidazole derivatives were synthesized (In 1991) by derivatization at N-H of benzimidazole by electron donating group and substitution with long chain of propyl, acetamido, thio, thiazole-amino, tetramethylpiperidine on pyridine resulting in good antiulcer activity.[12,13]

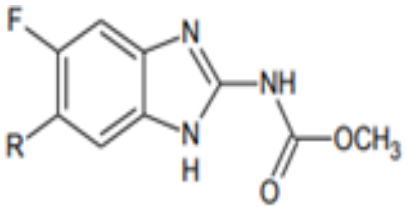
They are used in clinical medicine Based on their broad biological functions as anti-ulcer, anti- tumor and anti-viral agents.[14]

A. Michiletonilliet. al, synthesized antiviral activity of Benzimidazole derivatives. Antiviral activity of 2-phenylbenzimidazole derivatives.[15]



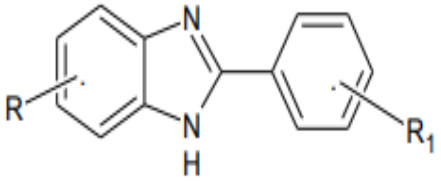
Heteroaryl = furan-3-yl; pyridin-2-yl R’ = OH, NH-R

B. KUS Canan, Synthesis of Some New BenzimidazoleCarbamate Derivatives for Evaluation of Antifungal Activity.[16]

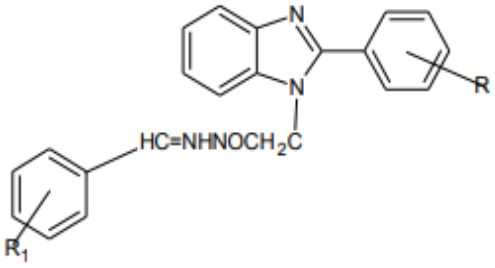


R= Cl, 4-morpholinyl, 1-pyrrolidinyl, 3- methylpiperidin-1-yl, (pyridin-3-ylmethyl)- amino.

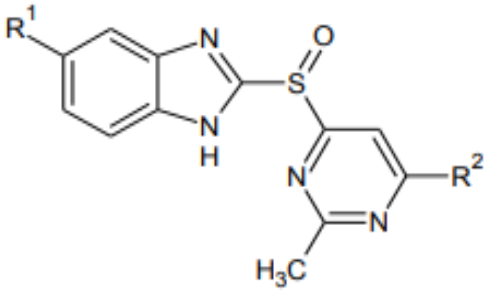
C. DT Nannapaneni, Atyam VSSS Gupta, MI Reddy, and RaiduChSarva et.al., Synthesis, Characterization, and Biological Evaluation of Benzimidazole Derivatives as Potential Anxiolytics.[17]



D. Balram Soni, Mahendra Singh Ranawaet.al., synthesis and in vitro antitumor activity of benzimidazole derivatives.[18]



E. Khan Farhan. R., Asnani A. J.et.al., Synthesis and Antiulcer, Anti-secretory Activity of Some New substituted 2-(Pyrimidinylsulfinyl) Benzamidazole Derivatives.[19]



3. Experimental section

All chemicals were purchased from LOBA CHEMIE Solvents used for the chemical synthesis acquired from commercial sources were of analytical grade and were used without further purification unless otherwise stated. Reactions were monitored by TLC, which was performed with preparative TLC method on glass slide. NMR spectra were recorded on Bruker Advance DPX (400 MHz) spectrometer. Chemical shift are reported in parts per million (ppm) units relative to tetramethylsilane (TMS) as internal standard. Coupling constant (*J*) are reported in Hertz (Hz).

4. Synthesis of benzimidazole

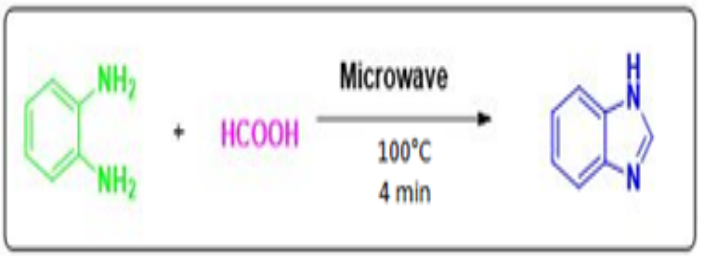
A. Conventional method for synthesis of benzimidazole

Procedure

- *o*-phenylenediamine (0.25 mol) and 90 per cent formic acid (0.34 mol) was placed in a 250 ml round bottom flask.
- It was heated on water bath for 2 hr at 100°C (reaction mixture monitor by TLC)
- Cooled and added 10% NaOH slowly with constant rotation of flask (until the reaction mixture is alkaline to litmus)
- Filter and wash with 25 ml water.
- Crude product was dissolved in 400 ml of boiling water + 2g of decolourising carbon (charcoal) for 15 min. filter it and filtrate allowed to cool in ice water to get pure benzimidazole.

Time (Min)	Yield (%)
30 min	NR
60 min	NR
90 min	NR
120 min	74
150 min	84.56
180 min	85

B. Microwave assisted synthesis of benzimidazole



Procedure

- *o*-phenylenediamine(0.25 mol) and 90 per cent formic acid (0.34 mol) placed in a 250 ml round bottom flask.

- The mixture was heated in microwave at 100 °C for 4 minutes. (Reaction mixture monitor by TLC).
- Cooled and added 10% NaOH slowly with constant rotation of flask (until the reaction mixture is alkaline to litmus)
- Filter and it was washed with 25 ml of water
- Crude product was dissolved in 400 ml of boiling water, added 2g of decolourising carbon (charcoal) for 15 min. filter it and filtrate allowed to cool in ice water to get pure benzimidazole.

Time (min)	Yield (%)
2	No reaction
4	90
6	88
8	91
10	90

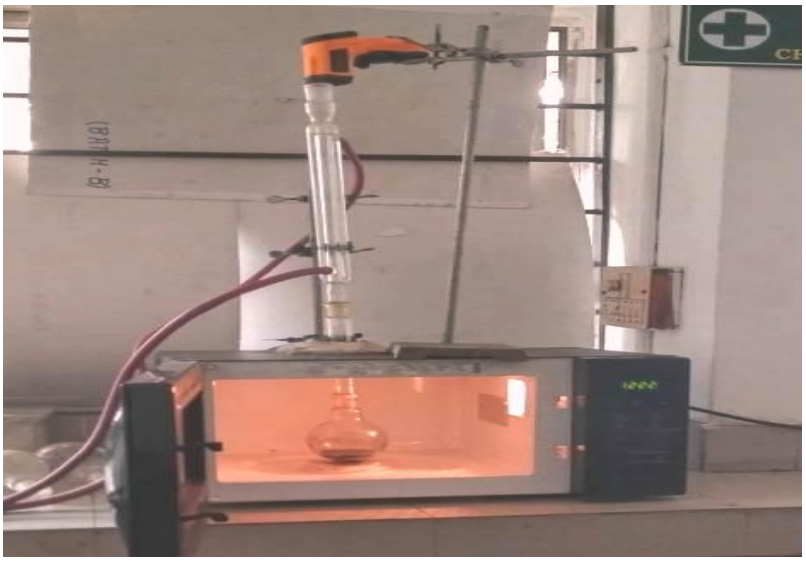


Fig. 2:- Microwave assisted synthesis.

5. Purification

Product was confirmed by TLC using Ethyl acetate: Hexane (5:5) and purification was done by column chromatography.

Fig. 3:- TLC.

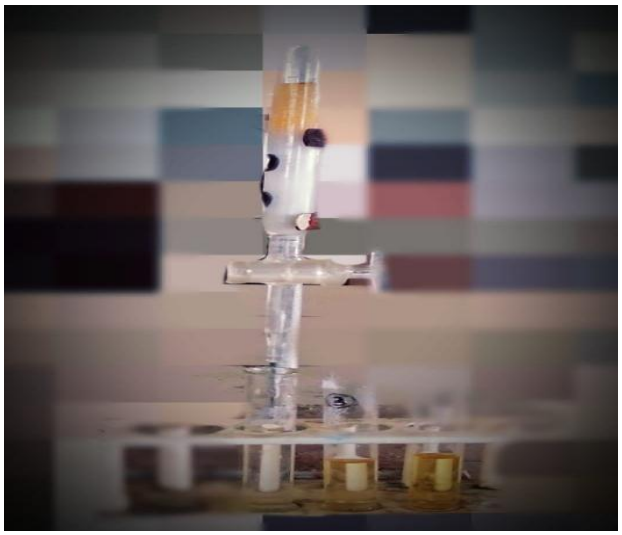


Fig. 4:- Column separation.

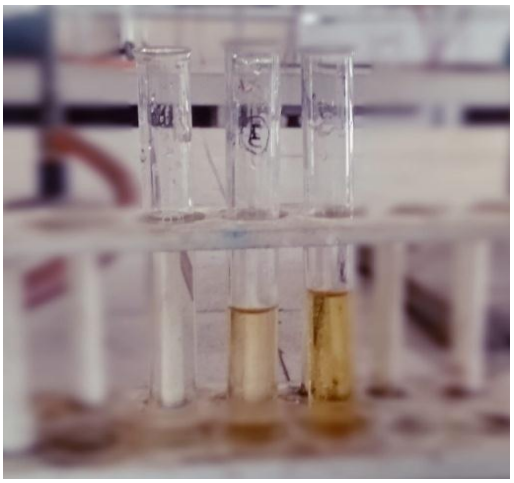


Fig. 5:- Separated component fluids.

Fig 6:- Workup.

6. Characterization

A. Priliminary studies

Tests	Observations	Inference
State	Solid	Crystalline in nature
Colour	Creamish white	-
Odour	Odourless	-
Flame tests	Non-luminous flame	Aromatic in nature
Soda lime Test	Liberation of ammonia	Amides are present
Litmus paper test	Red litmus turning blue	Basic in nature
Solubility Test	Insoluble in water	-

B. Functional group detection.

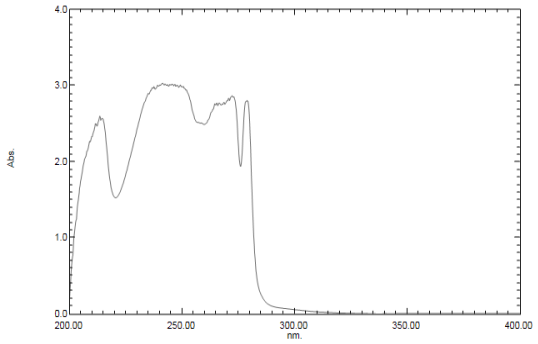
Test	Observation	Infeence
Take smple, add about 5 ml of 10% sodium hydroxide solution and boil.	Ammonia was evolved	Amide present

C. Element detection.

Test	Observation	Inference
Test for nitrogen: Take 1-2 ml filtrate and add few crystals of ferrous sulphate. Boil gently, acidify with dilute sulphuric acid.	Greenish blue colour ppt was observed	Nitrogen was present

7. Spectroscopical study

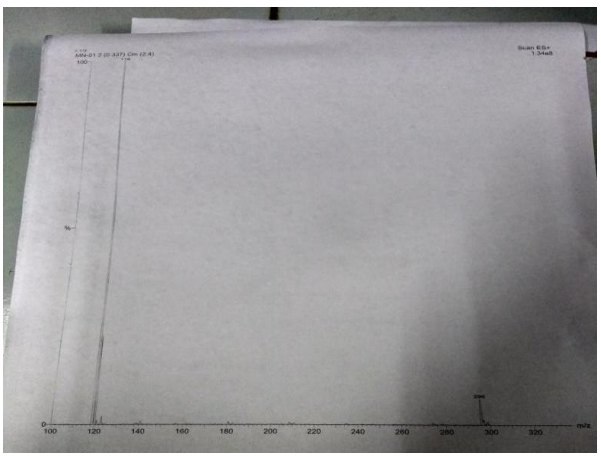
➢ UV spectroscopy

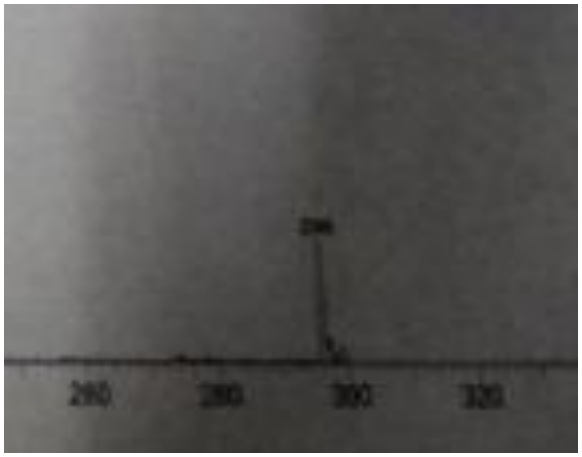


No.	P/V	Wavelength	Abs.	Description
1	↑	340.20	0.0	
2	↑	332.00	0.0	
3	↑	278.80	2.8	
4	↑	272.20	2.9	
5	↑	266.40	2.8	
6	↑	250.60	3.0	
7	↑	241.40	3.0	
8	↑	213.40	2.6	
9	↓	343.00	-0.0	
10	↓	337.80	-0.0	
11	↓	276.00	1.9	
12	↓	267.40	2.7	
13	↓	260.00	2.5	
14	↓	248.40	3.0	
15	↓	220.40	1.5	

❖ Benzimidazole shows λmax at 213.40 nm

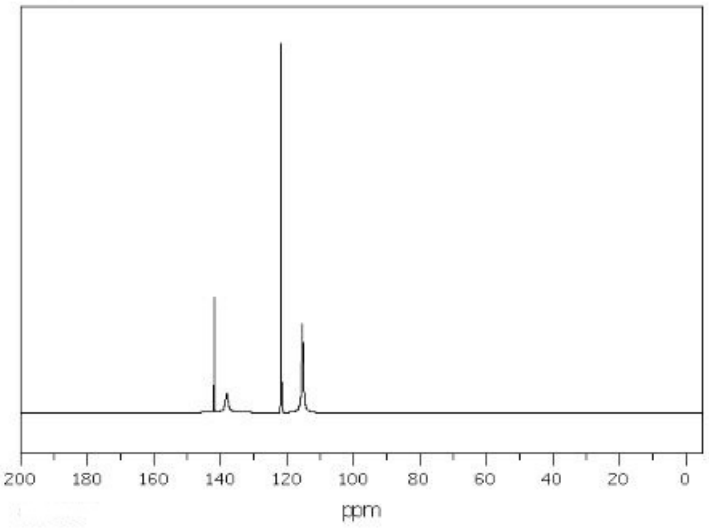
➢ Mass spectroscopy



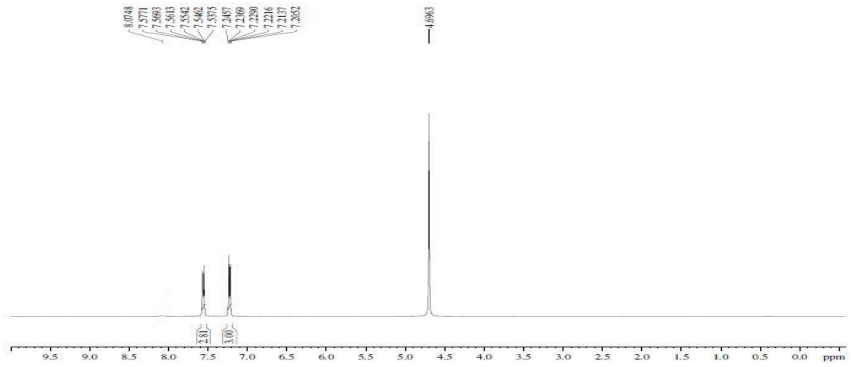


❖ Calculated m/z is 118.139 and found m/z of the given sample is 119.

- C-NMR

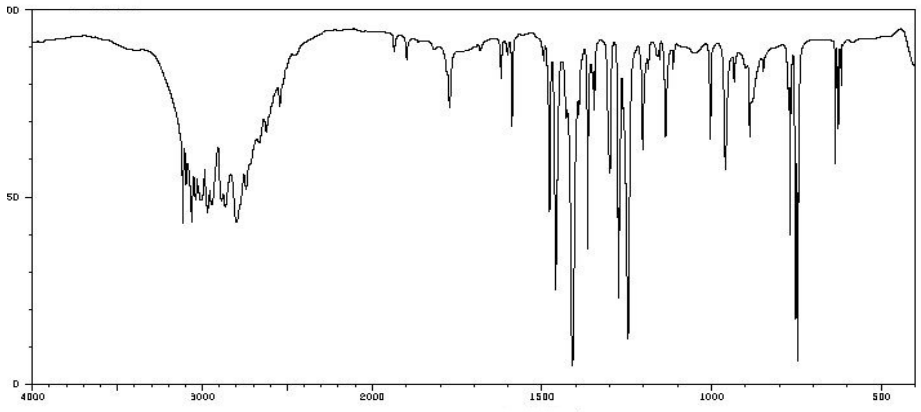


- H-NMR



❖ 1 H NMR (400 MHz, $CDCl_3$) δ 7.6 (t, 2H), 7.2 (s, 3H), 4.7 (s, 1H).

- IR



❖ The IR value of NH stretch found to be 3100 cm^{-1}

8. SUMMARY

- The synthesis of benzimidazole from *o*- phenylenediamine by conventional method was affordable but it has given less yield as compared to microwave assisted synthesis.
- The conventional method is a time consuming process.
- The microwave assisted synthesis of benzimidazole has given good yield i.e. 95%.
- The benzimidazole synthesis was preliminary confirmed by TLC using Ethyl acetate: Hexane (50:50) as a mobile phase.
- Again it was confirmed by element detection and functional group detection.
- Element detection shows the presence of nitrogen and functional group detection confirmed the presence of amine.
- Final confirmation was done by spectroscopic method i.e. UV, IR, NMR, MASS.

9. CONCLUSION

- The microwave assisted synthesis of benzimidazole is more efficient than the conventional method of synthesis.
- The microwave assisted synthesis is very less time consuming method (i.e. the reaction completed within 4 min).
- Microwave assisted synthesis give more yield than the conventional synthesis method.
- In microwave assisted synthesis there is no loss of reactant compounds during reaction.

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