Microwave-Assisted Synthesis of Nitrogen Heterocycles: Advancements, Mechanistic Insights, and Biological Evaluations

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Abstract— Microwave-assisted synthesis has emerged as a revolutionary technique within organic chemistry, revolutionizing the fabrication of a wide array of nitrogen heterocycles. This abstract provides an overview of the synthesis of nitrogen-containing heterocyclic compounds, utilizing microwave irradiation as a central methodology. By harnessing the power of microwave irradiation, reaction rates are accelerated, leading to enhanced yields and superior selectivity compared to conventional thermal methods. The synthesis of nitrogen heterocycles, including but not limited to pyrazoles, pyridines, triazoles, and pyrimidines, under microwave conditions will be explored, emphasizing the inherent advantages of this approach in terms of reaction efficiency and environmental impact mitigation. Furthermore, the elucidation of mechanistic insights pertaining to microwave-assisted synthesis of nitrogen heterocycles will be discussed, aiming to provide a comprehensive understanding of the underlying reaction pathways. Ultimately, microwave-assisted synthesis stands as a promising methodology for the swift and sustainable fabrication of nitrogen heterocyclic compounds, with broad-reaching applications spanning pharmaceuticals, agrochemicals, and materials science.

I. INTRODUCTION

Organic chemistry has many applied branches which are used in developing novel molecules. The most important and unique among them is heterocyclic chemistry especially based on nitrogen heterocyclic. Increasing attention has been given to this field in recent two decades of the present third millennium. Great contributions in the form of synthesis of novel organic molecules which have found wide applications as drugs [1] has come. Broad distribution of nitrogen heterocycles are found in nature. They have many pharmacological and physiological properties. Biologically important molecules have these heterocyclic moieties as their constituents. They include nucleic acids, vitamins, antibiotics, pharmaceuticals, agrochemicals and dyes [2]. They constitute integral part of many molecules which are pharmacologically active.

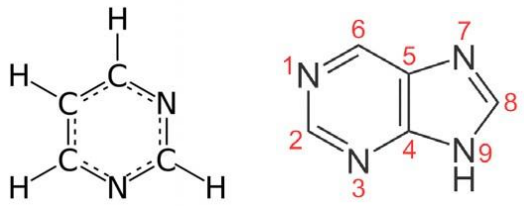


Fig-1

DNA and RNA are two important components of life. They need base pairs such as guanine, adenine, cytosine and thymine for their constitution. These are also constituted of heterocyclic compounds having nitrogen as one of heteroatoms. Purines and pyrimidines are two important heterocycles. The structures of these are shown in Fig.-(1) these molecules have different characteristics. They have gained importance due to their diverse applications.

Consequently fields of organic and medicinal industry are burgeoning [3]. From literature survey it is revealed that the most important active moiety among nitrogen heterocycles is benzimidazole. It contains a pair of nitrogen atoms which are present at nonadjacent positions. 4 One of the most burning problems of the present era is mental tension causing high blood pressure and leading to cardiovascular health hazards not only in senior citizens but also in youths. The most common and successful drug having minimum side effect is telmesartan which has a pair of benzimidazole moiety[4]. This has attracted attention on study on synthesis and characterization of

benzimidazole derivatives. Consequently, a program to synthesize and charactetize a series of benzimidazole derivatives leading to evaluation of their biological activity has been undertaken.

II. OBSERVATION

1.1 Methodology

Monitoring of Synthetic Reaction Procedures: Synthetic procedures were employed for synthesis of compounds BZ1 to BZ15 and the completion of reactions were monitored by Thin Layer Chromatography (TLC). Silica gel G is used as a adsorbent, the plates were activated by heating at 110° C for one hour[5]. Methanol: water, Methanol: Chloroform mixtures (9:1, 8:2, 7:3) were used as a Mobile phase. The plates were visualized by UV light, iodine chamber.

Purification Techniques: Recrystallization: The crude products were recrystallized by charcoal treatment with appropriate solvent. Single solvent was used wherever possible and solvent mixtures were not used anywhere.

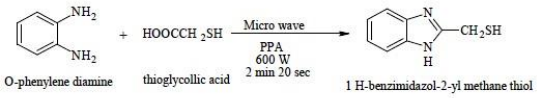
Authentication of Chemical Structures and Purity of Compounds: Chemical structure of synthesized compounds and their purity were identified by thin layer chromatography, UV visible spectrometer, melting point and various spectral techniques including Fourier Transform Infra Red Spectroscopy, Nuclear Magnetic Resonance Spectroscopy, Mass Spectroscopy and Ultra Violet Spectrophotometry.

1.2. Synthesis of compounds:

1.2.1. Synthesis of 1 H-benzimidazol-2-yl methane thiol: (BZ1)

a. Conventional method: O-phenylene diamine 27 g (0.25 M) and thioglycollic acid 31.28 g (0.34 M) was heated on a water bath at 100o C for 6-8 h. The completion of reaction was monitored by TLC. After completion of reaction, the reaction mixture was cooled and basified to a pH of 7-8 by using of 10% sodium hydroxide solution[6]. The crude benzimidazole was filtered at the pump, 66 washed with ice cold water. The crude product was dissolved in 400 ml of boiling water and 2 g of decolorizing carbon was added, digested for 15 min. The solution was filtered while hot, cooled the filtrate to about 10oC. The pure product was filtered, washed with 25 ml of cold water and dried at 100oC. (Vogel's 2006, Ahuluwalia et al., 2000) b.

Microwave method: O-phenylene diamine 1.08 g (0.01 M), thioglycollic acid 0.92 g (0.01 M) and poly phosphoric acid 10 g was properly mixed with glass rod in a beaker. The mixture was irradiated in the microwave oven for 2 min 20 sec at 600 W. The completion of reaction was monitored by TLC, after irradiation the mixture was poured into ice cold water and then slowly neutralized with sodium hydroxide to pH 8. The precipitate was collected by filtration, dried and recrystallized from hot water. (Rishipathak et al., 2007, Perumal et al., 2004)



Scheme- 1.b: Synthesis of 1 *H*-benzimidazol-2-yl methane thiol

1.2.2. Synthesis of 2-(propan-2-yl)-1H-benzimidazole (BZ2) :

a. Conventional method: O-phenylene diamine 27g (0.25 M) and isobutyric acid 29.92g (0.34 M) was heated on a water bath at 100oC for 6-8 h. The completion of reaction was monitored by TLC. After completion of reaction, the reaction mixture was cooled and basified to a pH of 7-8 by using of 10% sodium hydroxide solution. The crude benzimidazole was filtered at the pump, washed with ice cold water. The crude product was dissolved in 400 ml of boiling water and 2g of decolorizing carbon was added, digested for 15 min[7]. The solution was filtered while hot, cooled the filtrate to about 10oC. The pure product was filtered, washed with 25 ml of cold water and dried at 100oC. (Vogel's 2006, Ahuluwalia et al., 2000)

b. Microwave method: O-phenylene diamine 1.08 g (0.01 M), isobutyric acid 0.88 g (0.01 M) and poly phosphoric acid 10 g was properly mixed with glass rod in a beaker[7]. The mixture was irradiated in the microwave oven for 1 min 30 sec at 600 W. The completion of reaction was monitored by TLC, after irradiation the mixture was poured into ice cold water and then slowly neutralized with sodium hydroxide to pH 8. The precipitate was collected by filtration, dried

and recrystallized from hot water. (Rishipathak et al., 2007, Perumal et al., 2004)

1.2.3. Synthesis of 2-butyl-1H-benzimidazole: (BZ3)
a. Conventional method: O-phenylene diamine 27 g(0.25M) and valeric acid 34.68 g (0.34 M) was heated on a water bath at 100o C for 6-8 h. The completion of reaction was monitored by TLC. After completion of reaction, the reaction mixture was cooled and basified to a pH of 7-8 by using of 10% sodium hydroxide solution. The crude benzimidazole was filtered at the pump, washed with ice cold water. The crude product was dissolved in 400 ml of boiling water and 2 g of decolorizing carbon was added, digested for 15 min. The solution was filtered while hot, cooled the filtrate to about 10oC. The pure product was filtered, washed with 25 ml of cold water and dried at 100o C. (Vogel's 2006, Ahuluwalia et al., 2000)

b. Microwave method: O-phenylene diamine 1.08 g (0.01 M), valeric acid 1.02 g (0.01 M) and poly phosphoric acid 10 g was properly mixed with glass rod in a beaker[8]. The mixture was irradiated in the microwave oven for 1 min 15 sec at 600 W. The completion of reaction was monitored by TLC, after irradiation the mixture was poured into ice cold water and then slowly neutralized with sodium hydroxide to pH 8. The precipitate was collected by filtration, dried and recrystallized from hot water. (Rishipathak et al., 2007, Perumal et al., 2004)

1.2.4. Synthesis of (1H-benzimidazol-2-yl) aniline: (BZ4)
a. Conventional method: A mixture of O-phenylene diamine 3.8 g (34 mM) and 4 amino benzoic acid 4.5 g (33 mM) were stirred in a syrupy O phosphoric acid (45 ml) at 200º C for 2 h. The reaction mixture was cooled and poured on to the crushed ice. The bulky white precipitate obtained was stirred in cold water (400 ml) and sodium hydroxide solution (5 M) was added until the pH 7. The resulting solid was filtered and recrystallized from methanol. (Sreena et al., 2009)

b. Microwave method: O-phenylene diamine 1.08 g (0.01 M), 4-amino benzoic acid 1.37 g (0.01 M) and poly phosphoric acid 10 g was properly mixed with glass rod in a beaker. The mixture was irradiated in the microwave oven for 6 min 30sec at 600W[9]. The completion of reaction was monitored by TLC, after irradiation the mixture was poured into ice cold water and then slowly neutralized with sodium hydroxide to pH8. The precipitate was collected by filtration, dried and recrystallized from methanol. (Rishipathak et al., 2007, Perumal et al., 2004)

1.2.5. Synthesis of 2-(4-nitrophenyl)-1H-benzimidazole: (BZ5)
a. Conventional method: O-phenylene diamine 1.08 g (0.01 M) and 4-nitro benzoic acid 1.69 g (0.01 M) in 20 ml acetic acid was refluxed for 4h. The precipitate obtained after cooling was recrystallized from ethanol. (Mohamed al messmary et al., 2010)

b. Microwave method: O-phenylene diamine 1.08 g (0.01 M), 4-nitro benzoic acid 1.69g (0.01M) and poly phosphoric acid 10g was properly mixed with glass rod in a beaker. The mixture was irradiated in the microwave oven for 8 min 30sec at 600 W. The completion of reaction was monitored by TLC, after irradiation the mixture was poured into ice cold water and then slowly neutralized with sodium hydroxide to pH 8. The precipitate was collected by filtration, dried and recrystallized from ethanol. (Rishipathak et al., 2007, Perumal et al., 2004)

III. RESULT

Evaluation of in vitro anti-bacterial activity: The synthesized compounds (BZ11-BZ15) were tested for anti-bacterial activity by disc diffusion method. They were dissolved in DMSO and sterilized by filtering through 0.45 µm millipore filter. A final inoculum of 100 µl suspension containing 108 CFU/ ml of each bacterium was used. Nutrient agar medium was prepared and sterilized by an autoclave (121ºC and 15 lbs for 20 min) and transferred to previously sterilized petridishes (9 cm in diameter). After solidification, petriplates were inoculated with gram negative bacterial organisms Proteus vulgaris NCTC 4635, Klesibella pneumonia ATCC 29655 and gram positive bacterial organisms Bacillus cereus NL98, Enterococcus faecium ATCC 29212 in sterile nutrient agar medium at 45o C under aseptic condition. Sterile whatmann filter paper discs (previously sterilized in U.V. lamp) were impregnated with synthesized compounds at a concentration of 25, 100 µg/disc were placed in the organism impregnated petri plates under sterile condition. The plates were left for 30 min to

allow the diffusion of compounds at room temperature. Antibiotic disc of ciprofloxacin (100 µg /disc) was used as positive control, while DMSO used as negative control. Then the plates were incubated for 24 h at 37 ± 1o C. The zone of inhibition (Table-3) was calculated by measuring the minimum dimension of the zone of no microbial growth around the each disc. Evaluation of in vitro anti-fungal activity: The synthesized compounds (BZ11-BZ15) were tested for anti-fungal activity by disc diffusion method. They were dissolved in DMSO and sterilized by filtering through 0.45 µm millipore filter.

Synthetic Scheme: There are several methods reported for synthesis of 2 substituted benzimidazole derivatives. Mainly two methods are widely employed, which are coupling of O-phenylene diamine with different substituted organic acid in the presence of strong acidic medium (it also done through microwave irradiation) and the coupling of O-phenylene diamine with different substituted aldehydes.

CONCLUSION

Microwave-assisted synthesis has emerged as a groundbreaking approach in organic chemistry, particularly within the domain of heterocyclic chemistry. This investigation highlights the effectiveness of microwave irradiation in accelerating reaction rates and improving yields, presenting a compelling alternative to traditional thermal methods. By synthesizing a diverse range of nitrogen-containing heterocyclic compounds, including pyrazoles, pyridines, triazoles, and pyrimidines, microwave irradiation showcases its superiority in both reaction efficiency and environmental sustainability.

Moreover, this study delves into the mechanistic intricacies underlying microwave-assisted synthesis, offering valuable insights that pave the path for future advancements in this field. The successful synthesis and characterization of benzimidazole derivatives, as evidenced by compounds BZ1 to BZ15, underscore the versatility and promise of microwave-assisted synthesis in drug discovery and development.

Furthermore, the assessment of the synthesized compounds for their biological activity against bacteria and fungi underscores the practical significance of microwave-assisted synthesis in pharmaceutical research. These findings collectively affirm microwave-assisted synthesis as a promising methodology for the swift and eco-friendly production of nitrogen heterocyclic compounds, with wide-ranging applications across industries such as pharmaceuticals, agrochemicals, and materials science. Consequently, continued exploration and refinement of microwave-assisted synthesis techniques hold immense potential for catalyzing innovation and advancing the boundaries of organic chemistry in the years to come.

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