# Preparation of Benzimid Azolyl Pyrazole Derivatives Using Microwave Irradiation and Assessment of Their Antimicrobial Properties

***Dr. Beena Agarwal**

**Abstract**

A highly effective and convenient method has been developed to efficiently synthesize a range of pyrazole derivatives using microwave irradiation. The process involves the reaction between benzimidazolyl chalcone (1) and bromine in chloroform, resulting in the formation of dibromochalcones (2). These dibromochalcones are then further reacted with hydrazine hydrate to produce the desired compounds, specifically 3-benzimidazolyl-5-aryl-2-pyrazoles (3). Thorough characterization of the synthesized compounds was conducted using elemental analysis, as well as spectroscopic techniques such as IR, NMR, and MS.

The utilization of microwave irradiation significantly improved the yield of the target products while reducing the overall reaction time. This method offers great efficiency and convenience compared to traditional approaches. Moreover, the synthesized pyrazoles were subjected to antimicrobial screening in vitro, revealing promising biological activity for certain compounds.

**Introduction**

Advancements in chemical reaction techniques have led to the development of environmentally friendly methods that prioritize sustainability. Microwave irradiation has emerged as a valuable approach for accelerating organic reactions, offering numerous advantages compared to traditional methods. The utilization of microwave energy allows for the swift and convenient synthesis of intricate molecules that would typically necessitate prolonged reaction durations. This technique offers benefits such as reduced reaction time, simplified work-up procedures, and cleaner product formation, making it highly advantageous for chemical synthesis. Moreover, microwave-assisted reactions can be performed without the need for solvents, which is particularly significant as many solvents are environmentally harmful and expensive. This solvent-free condition aligns with the principles of green chemistry and contributes to eco-friendly processes.

Chalcones, characterized by an α, β-unsaturated ketone system, play a crucial role as Michael acceptors and serve as building blocks for the synthesis of diverse biologically active compounds. These compounds are employed in the preparation of various heterocyclic and carbocyclic systems, including five, six, and seven-membered rings such as pyrazolines, isoxazolines, pyridines, pyrimidines, diazepines, and thiazepines. The synthesis of heterocyclic compounds containing

pyrazole rings has attracted considerable interest owing to their extensive array of pharmacological properties. Pyrazole derivatives possess a wide spectrum of pharmacological activities, antiepileptic, antiviral, anti-inflammatory, antihypertensive, antidepressant, anticancer effects, and encompassing analgesic. Their pharmacological versatility positions them as promising candidates for the discovery and development of novel therapeutic agents.

Considering the aforementioned findings and the significant contribution of the benzimidazole nucleus in the synthesis of bioactive heterocyclic compounds, it was deemed valuable to investigate the bromination of 1-benzimidazolyl-3-aryl-2-propen-1-ones. The primary objective of this investigation was to produce novel dibromo chalcones that could function as intermediates for the synthesis of pyrazole derivatives with prospective pharmacological properties.

To initiate the synthesis, the necessary precursor, namely 1-benzimidazolyl-3-aryl-2-propenone [1a-f], was obtained through a condensation reaction. Specifically, the compound 2-acetyl benzimidazole was subjected to a condensation reaction with different aromatic aldehydes, each bearing diverse substituents. This reaction resulted in the formation of 1-benzimidazolyl-3-aryl-2-propenone derivatives [1a-f]. The reaction took place under solvent-free solid-phase conditions, utilizing microwave irradiation and a base such as NaOH or KOH. This approach, which has been previously reported in the literature, offers advantages such as accelerated reaction rates, enhanced product yields, and reduced environmental impact.

By employing this innovative method, the desired compounds were synthesized efficiently and in a more environmentally friendly manner. The brominated chalcones obtained from this process could then be further transformed into pyrazole derivatives, which hold great potential for various pharmacological activities. This research contributes to the exploration of novel synthetic routes and the development of biologically active compounds, ultimately advancing the field of medicinal chemistry.

**Methodology**

Using an electrothermal apparatus, the melting points of all produced compounds were calculated. The observations were taken in open capillary tubes. It's crucial to remember that these melting points are supplied as-is. On aluminum plates with silica gel coatings, thin-layer chromatography was carried out to keep track of the compounds' purity and the development of the reactions. The visualization was done using UV light. Additionally, a UV-Vis spectrophotometer, especially the UV-1700 model from Shimatzu, was used to monitor the reactions' progress. The structures of the produced compounds were verified using a variety of analytical methods. Both spectral analysis and elemental analyses were done. Using KBr as the medium, infrared (IR) spectra were captured using a Perkin-Elmer spectrophotometer in the 4000-400 cm-1 range. A JEOL ECS 400 MHz NMR spectrometer was used to collect proton nuclear magnetic resonance (1H NMR) spectra using CDCl3 as the solvent and TMS (tetramethylsilane) as the internal standard for chemical shifts, expressed in ppm. An instrument called the Xevo G2-SQ, TOF (Waters), was used to record mass spectra (FAB). The

matrix used in matrix-assisted laser desorption/ionization (MALDI) analysis was m-nitrobenzyl alcohol.

It's important to note that the synthesis of all the chemicals was carried out in a home microwave oven (more precisely, a Samsung CE117ADE model with an output of 900 W and a frequency of 2450 MHz). The use of these analytical methods allowed us to characterize the synthesized compounds, judge their purity, and track the development of the reactions. This knowledge on the structural characteristics of the compounds allowed for further investigation and interpretation.

**Preparation of 2a-f: 1- benzimidazolyl-3-aryl-prop-2-ene-1-one-2,3- dibromides**

A solution of 1-benzimidazolyl-3-aryl-2-propenones (1a-f) in chloroform (25 ml, 0.01 mole) was prepared. To this solution, a solution of bromine (0.01 mole) in chloroform (25 ml) was added dropwise with continuous agitation. The reaction mixture was agitated for 30 minutes at ambient temperature after the complete addition of bromine. The resulting solid was separated by filtration, rinsed with chloroform, and subsequently precipitated from ethanol. This process yielded cream-colored solids (2a-f) in a range of 80-85% yield.

**Preparation of 3-benzimidazolyl-5-aryl-2-pyrazoles (3a-f)**

The benzimidazolyl chalcone dibromides (2) were dissolved in 20 ml of ethanol to form a 0.01 mole solution. Hydrazine hydrate was added to this solution in the amount of 0.01 mole and carefully stirred. Following the exposure of the reaction mixture to microwave irradiation at 300 watts for a duration of 3-5 minutes, the progress of the reaction was monitored using thin layer chromatography (TLC). Once the reaction completion was indicated by TLC, the contents were cooled to room temperature and carefully transferred into ice-cold water. The resulting solid was separated by filtration, washed with water, dried, and subsequently precipitated from ethanol. The obtained crystals, which were white in color, exhibited a yield ranging from 80% to 88%.

**RESULTS AND DISCUSSION**

The confirmation of the product's structure was achieved by conducting elemental analysis and analyzing spectral data. The infrared (IR) spectra of compounds (2a-f) exhibited characteristic stretching vibrations associated with the carbonyl group, which appeared in the range of 1680-1630 cm-1. Furthermore, distinct stretching bands attributed to aromatic (C-H) bonds were observed within the region of 3000-2900 cm-1. Absorption bands of medium intensity, associated with the vibration of the benzene ring, were detected in the range of 1600-1400 cm-1. The specific number and position of these peaks depended on the substitution pattern of the aromatic rings. Additionally, a medium intensity peak corresponding to C-Br stretching was observed in the region of 650-550 cm-1.

The 1H NMR spectra of compounds (2a-f) demonstrated doublets for the C-H protons, with chemical shifts ranging from δ 5.64-5.67 (Hα) and 6.44-6.49 (Hβ). A multiplet in the chemical shift range of δ 6.89-8.01 was observed for the aromatic protons. The mass spectra (FAB) of the dibromide

compounds showed molecular ion peaks corresponding to their respective molecular masses. Fragmentation of the compounds generally occurred as anticipated, resulting in the generation of ions on both sides of the carbonyl group. The specific ions generated depended on the substitution pattern of the progenitor compound. In the IR spectra of compounds (3a-f), distinctive absorption bands were observed at 3350 cm-1, corresponding to -NH stretching, and at 2986-2800 cm-1, corresponding to C-H stretching. Additionally, a broad band in the range of 1444-1361 cm-1 indicated the combined vibration of C=N and C=C groups.

The 1H-nuclear magnetic resonance (NMR) spectra of compounds (3a-f) revealed the presence of a doublet at the chemical shift range of 2.04-2.7, indicating the existence of hydrogen atoms at position C4 of the pyrazole ring. The aromatic protons exhibited a multiplet with chemical shifts spanning from δ 7.22 to 7.89. The mass spectra confirmed the presence of molecular ion peaks corresponding to the molecular masses of the compounds. Furthermore, the mass spectra provided evidence implying that the formation of pyrazole likely involved the intermediate formation of 4-bromo-pyrazoline (3"), which subsequently underwent dehydrobromination to yield the desired pyrazole structure. (Refer to Tables 1-3 for additional information.)

**Table 1. Physical characteristics of 1-benzimidazolyl-3-aryl-prop-2-ene-1-one-2,3-dibromide compounds (2a-f)**

| Compound | AR | Molecular Formulae (Mol.Wt.) | Melting Point (°C) | Percent yield (%) | Average Duration (hrs) |
|---|---|---|---|---|---|
| **2a** | Phenyl | $C_{16}H_{12}N_2OBr_2$ (408) | 145 | 84 | 5.0 |
| **2b** | 4-methoxy phenyl | $C_{17}H_{14}N_2O_2Br_2$ (438) | 165 | 83 | 6.0 |
| **2c** | 3,4-dimethoxyphenyl | $C_{18}H_{16}N_2O_3Br_2$ (468) | 227 | 87 | 5.0 |
| **2d** | 3,4,5-trimethoxyphenyl | $C_{19}H_{18}N_2O4Br_2$ (498) | 112 | 82 | 6.0 |
| **2e** | 4-chlorophenyl | $C_{16}H_{11}N_2O5Br_2$ (442.5) | 132 | 83 | 5.0 |
| **2f** | 2-furanyl | $C_{13}H_{10}N_2OBr_2$ (386) | 111 | 85 | 5.5 |

**Table 2. Physical characteristics of 3-benzimidazolyl-5-aryl-2-pyrazoles (3a-f)**

| Compound | AR | Molecular Formulae (Mol.Wt.) | Melting Point (°C) | Percent yield (%) | Average Duration (hrs) |
|---|---|---|---|---|---|
| **3a** | Phenyl | $C_{16}H_{12}N_4$ (260) | 167 | 89 | 4 |
| **3b** | 4-methoxy phenyl | $C_{17}H_{14}N_2O_2$ (290) | 143 | 87 | 4.5 |
| **3c** | 3,4-dimethoxyphenyl | $C_{18}H_{16}N_2O_3$ (320) | 155 | 88 | 4 |
| **3d** | 3,4,5-trimethoxyphenyl | $C_{19}H_{18}N_2O_3$ (350) | 114 | 89 | 4.5 |
| **3e** | 4-chlorophenyl | $C_{16}H_{11}N_2Cl$ (294.5) | 98 | 82 | 3.5 |
| **3f** | 2-furanyl | $C_{14}H_{10}N_4O$ (386) | 124 | 81 | 4 |

**Table 3. Antibacterial activity evaluation of compounds (3a-f) by measuring the diameter of inhibition zones**

| Compound | Antifungal | | | AntiBacterial | | |
|---|---|---|---|---|---|---|
| | **C. albicans** | **A. niger** | **E. coli** | **K. pneumonia** | **K. pneumonia** | **P. aeruginusa** |
| **3(a)** | 17 | 14 | 16 | 7 | 15 | 14 |
| **3(b)** | 11 | 12 | 11 | 7 | 13 | 14 |
| **3(c)** | 17 | 14 | 12 | 11 | 15 | 11 |
| **3(d)** | - | - | 14 | 9 | 13 | 11 |
| **3(e)** | 16 | 13 | 12 | 11 | 15 | 14 |
| **3(f)** | 17 | 11 | 14 | 8 | 14 | 19 |
| **Standard Diflucan** | 17 | 12 | - | - | - | - |
| **Standard Coffrioxane** | - | - | 20 | 22 | 23 | 24 |

The identification of the synthesized products was based on their analytical and spectral data, as well as confirmation through CO-TLC (Thin Layer Chromatography) and melting point measurements (Table 1). The results demonstrate that the microwave irradiation (MWI) method enables for effective reactions with high yields and reduced reaction times (Table 2). To evaluate the

antimicrobial activity of the newly prepared compounds, they were evaluated against Candida albicans and Aspergillus niger for antifungal activity, and against E. coli, P. aeruginosa, B. subtilis, and K. pneumoniae for antibacterial activity. The screening was conducted in vitro using a concentration of 300 mg/ml. Diflucan and coffrioxane were used as standard medications for the respective assays. The obtained results are presented in Table 3. In these experiments, the inhibition zones were measured to assess the efficacy of the compounds against the target microorganisms. Larger inhibition zones indicate increased antimicrobial activity.

**Conclusion**

The newly synthesized compounds exhibited satisfactory elemental data. In comparison to the traditional approach, the microwave-assisted synthesis procedure exhibited significant acceleration, reducing the reaction time from hours to minutes and resulting in enhanced yields. This inventive method offers a simplified laboratory technique by eliminating the need for standard organic laboratory apparatus such as reflux condensers and stirrers. The solid-phase, solvent-free microwave method was chosen over the liquid-phase method due to its advantages of eliminating the use of costly and hazardous solvents. This approach is not only cost-effective and convenient but also environmentally benign, aligning with the principles of green chemistry.

***Associate Professor**
**Department of Chemistry**
**Government College**
**Tonk (Raj.)**

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