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Optimization of Microwave Assisted Synthesis of Substituted Imidazoles–A Green Approach

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ABSTRACT

The design of experiments, and optimization of the variables that might affect the yield or quality of the product has been widely used in pharmaceutical research. The objective of this study was to develop optimized conditions for the microwave-assisted synthesis of imidazole and their N-substituted derivatives by the use of optimization techniques. A 2^2 factorial design was employed for optimization using microwave power and microwave time as independent factors and percent yield as the response factor. Imidazoles 4a-m were synthesized using the optimized reaction conditions by reaction of benzyl, ammonium acetate, and aromatic aldehydes while N-substituted derivatives of 4a-m were synthesized in alkaline conditions by reaction with 2-chloromethyl pyridine.

Keywords: Debus-Radziszewski, Factorial design, Imidazole, Microwave optimization.

INTRODUCTION

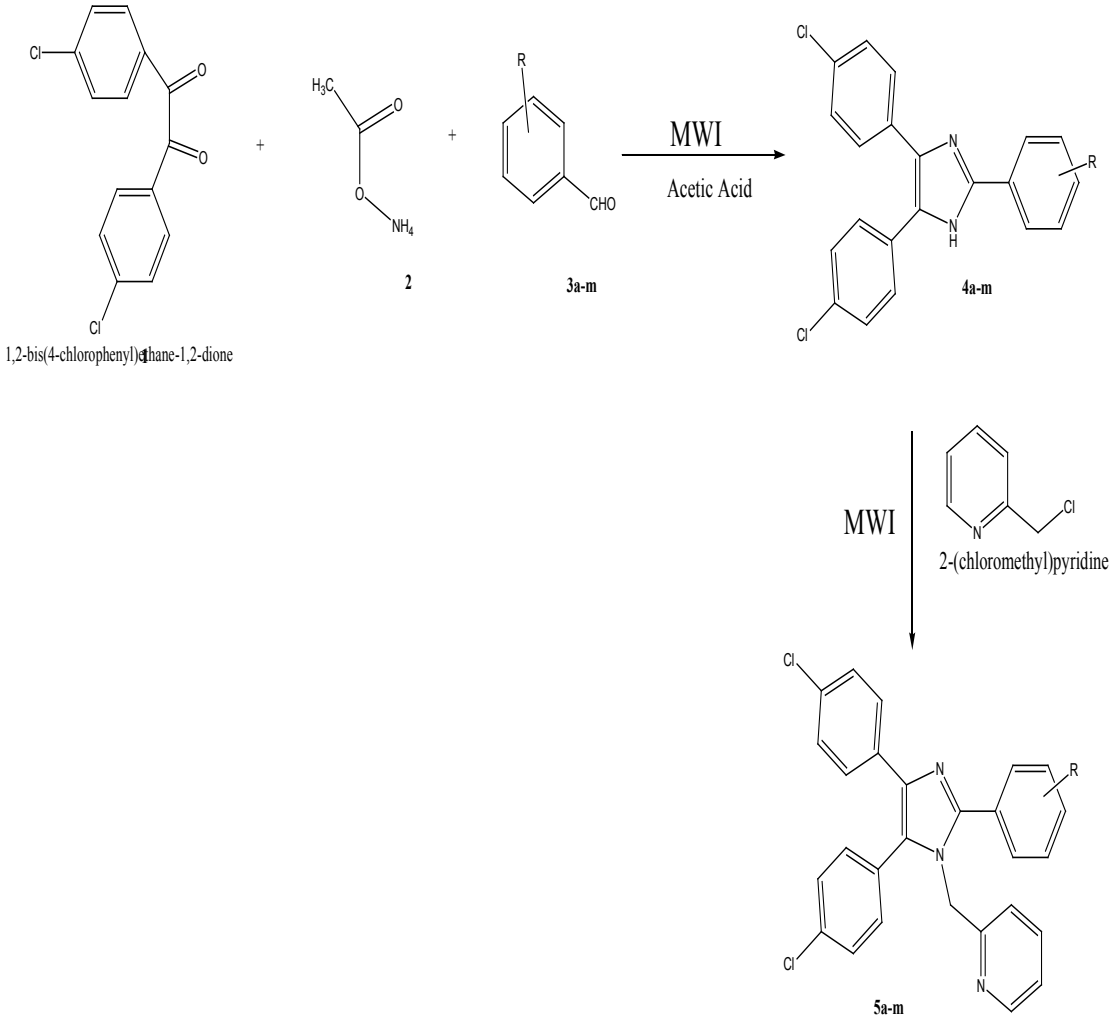
The fabrication of novel persuasive substances has always been of interest of the research community. A significant method for drug designing includes the alteration of the known substance and its recognized application.[1,2] Imidazole having IUPAC nomenclature as 1,3-diaza-2,4-cyclopentadiene, is a 5 member N-heterocyclic aromatic organic compound with two nitrogen atoms. The chemical formula of the compound is represented as $C_3H_4N_2$. Imidazole moiety is a promising fundamental and structural unit of therapeutic scaffolds.[3,4,5] Synthesis of a novel drug product, drug intermediate, or pharmaceutical process involves multiple steps procedures. All these procedures are time-consuming as the conventional methods of synthesis involve refluxing for several hours using a hot oil bath as the heating source followed by a tedious post-reaction workup for obtaining the pure product. This time can be reduced by optimization of the reaction conditions along with the use of microwave radiation instead of the conventional heating method. The utilization of microwave energy acts as an efficient heating source as it causes internal heating of the reactants owing to the dipole interactions of the microwave energy with the dipoles of the ions of the reactant molecules. This causes a significant reduction in the heating time required for attaining the energy of activation of the reaction.[6] Several researchers have synthesized imidazoles and their derivatives

for various pharmacological actions.[7-15] Very limited reports of microwave-assisted synthesis of imidazole derivatives have been found with severe limitations of the poor yield of the product.[16,17] From the literature, it was observed that there are four major conventional synthetic routes for imidazole and derivatives thereof. These include the synthesis involving nitrile formation (Van Leusen synthesis), cyclization (Wallach synthesis), or cyanates (Marckwald synthesis), and a multicomponent reaction named Debus-Radziszewski synthesis.[18] The present work aims to develop, an optimized method for microwave-assisted production of imidazole and its structural analog, using the Debus-Radziszewski synthesis route. The optimization could be performed using microwave power, time, and molar ratio of the reactants as the independent variables while the percentage yield, as the dependent variable.

EXPERIMENTAL

MATERIAL AND METHODS

The chemicals required for the synthesis were procured from Avra Chemicals and Sigma Aldrich. The solvents and reagents were procured from Rankem and Oxford Chemicals. All the reactants, reagents, and solvents were used as obtained. Melting point was performed by open capillary method. Thin layer chromatography was carried out employing TLC plates precoated with silica gel G_{F254}. A modified Debus-Radziszewski synthesis method was performed as per Scheme 1 reported by Hanoon *et al.,*.[19]



Scheme 1

The conventional method of synthesis involves heating 0.01 mol of 1,2-bis(4-chlorophenyl) ethane-1,2-dione, 0.05 mol ammonium acetate, and 0.01 mol of aromatic aldehyde in 25 mL of ethanoic acid under reflux (1-2 h), leading to the formation of 2,4,5-triphenyl-1H-imidazole. This imidazole is then reacted with 1-(2-chloroethyl)piperidine in an alkaline environment by refluxing for 4-6 hours.

The heating temperature, heating duration, and the molar ratio of the reactants have been the most critical elements for synthesis. Hence, the microwave power, and time were considered for optimization of the reaction method, keeping the molar ratio of the reactants constant in consonance with the original method. A 2^2 factorial approach was used for the optimization of the reaction method (Table 1).

Table 1: 2^2 factorial design table for step 1

Independent Variables	Level	
Microwave power (watt)	540	720
Time (min)	6	7

Table 2: 22 factorial design table for step 2

Independent Variables	Level	
Microwave power (watt)	180	540
Time (seconds)	60	90

The reaction was performed according to the conditions mentioned in Tables 1 and 2 and tested for completion with TLC using hexane-ethylacetate (8:2) as the solvent system. The yield of the product obtained was observed as the dependent variable. The process was optimized for compound **4a** and the optimized method was used for the synthesis of $\mathbf{4}_{\mathbf{a\text{-}m}}$. In the second step, based on molar reaction mentioned in the literature, the molar concentration of the reactants was replaced with the concentration of the base as the independent variable. The process was optimized for compound **5a**, and the optimized method was used for the synthesis of $\mathbf{5}_{\mathbf{a\text{-}m}}$.

The prepared compounds, $\mathbf{5}_{\mathbf{a\text{-}m}}$ were characterized for their identity by employing Fourier transform infrared (FTIR) technique, Proton-Nuclear magnetic resonance (^{1}HNMR), and analytical technique involving mass spectroscopy (MS). The solubility and melting point of the compounds $\mathbf{5}_{\mathbf{a\text{-}m}}$ was also determined.

RESULTS AND DISCUSSION

The conditions of the reaction route was optimized using a factorial design approach. The yield of product **4a**, was considered as the conclusive dependent variable of the reaction for step 1 (Table 3) while the yield of **5a** was decisive for step 2 (Table 4).

Table 3: Yield of 4a using factorial design experiment

S. No	Power	Time (sec)	Yield (%)
1	560	60	43
2	720	60	60
3	560	120	51
4	720	120	87

Table 4: Yield of 5a using factorial design experiment

S. No.	Power	Time (sec)	Yield (%)
1	180	60	22
2	540	60	14
3	180	90	79
4	540	90	11

Each of the variables was tested for yield and statistical analysis was performed to assess the optimized independent variables. For the synthesis of imidazoles, the experiment performed on **4a** exhibited maximum yield on a microwave power of 720 watts and a reaction time of 7 minute. The molar ratio of the reactants was kept constant at 1:5:1 (dione-ammonium acetate-aldehyde). The equation that exhibits the fit to the yield was generated using NCSS 2022 v22.0.3 trial version software.

Yield = -159.5+0.165625* Power+17.5* Time

The ANOVA for yield investigation for **4a** was performed and the output is described in (Table 5).

Table 5: ANOVA output for yield investigation of 4a

Factor	Squared value	No. of independent variable	Mean Value	F- distribution	Probability
Intercept	14520.25	1	14520.25		
Model	1008.5	2	504.25	5.587	0.2866
Power	702.25	1	702.25	7.781	0.2191
Time	306.25	1	306.25	3.393	0.3166
Error	90.25	1	90.25		
Total (Adjusted)	1098.75	3	366.25		

After obtaining the significant model, the 3D-surface response plot (Fig. 1) was generated to understand the effect of each factor on yield more illustratively.

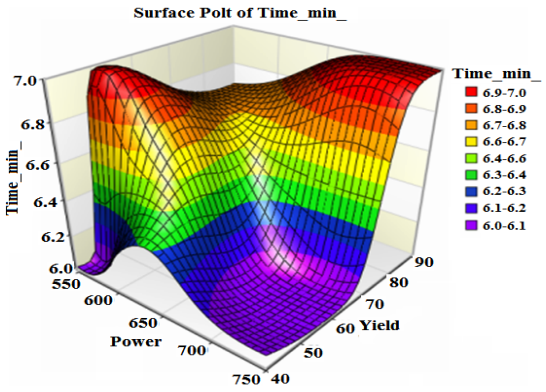


Fig. 1. 3D Contour plot for 4a

The predicted microwave time for a 100% yield of compound **4a**, at 720 watts microwave power was 5.7 minutes. The compounds $4_{a\text{-}m}$ were synthesized using the optimized reaction conditions predicted by the software and investigated for their yields. The formation of **5a** from **4a** exhibited maximum yield when the microwave power was 180 watt, and microwave time of 90 seconds. The molar ratio of all the reactants was kept constant as equimolar. The equation generated using multiple regression analysis to predict maximum yield was obtained using NCSS 2022 v22.0.3 trial version software.

Yield = 2-0.0155* Power+0.9* Time

The ANOVA for yield investigation for **5a** was performed and the output is described in Table 6.

Table 6: ANOVA output for yield investigation of 5a

Factor	Squared value	No. of independent variable	Mean Value	F- distribution	Probability
Intercept	3969	1	3969		
Model	2173	2	1086.5	1.207	0.5142
Power	1444	1	1444	1.604	0.4254
Time	729	1	729	0.810	0.5335
Error	900	1	900		
Total (Adjusted)	3073	3	1024.33		

After obtaining the significant model, the 3D-surface response plot, (Fig. 2) was generated to understand the effect of each factor on yield more illustratively.

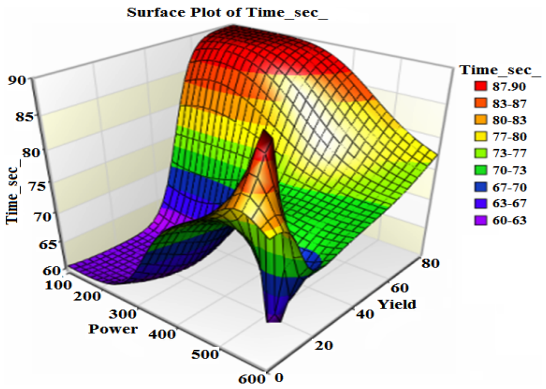


Fig. 2. 3D Contour plot for 5a

The predicted microwave time for a 100% yield of compound **5a** at 180 watts microwave power was 111 seconds.

Compounds $5^{a\text{-}m}$ were prepared using these optimized parameters and investigated for their yield.

2-((4,5-bis(4-chlorophenyl)-2-phenyl-1H-imidazol-1-yl)methyl)pyridine, 5a Yield: 79%; ^{1}HNMR (δ, ppm): 8.6 (C-H, adjacent to N of pyridine), 5.1 (C-H, methyl), 7.1-7.8 (C-H, aromatic); m/z: 456.1.

2-((2,4,5-tris(4-chlorophenyl)-1H-imidazol-1-yl)methyl)pyridine, 5b Yield: 74%; ^{1}HNMR (δ, ppm): 8.6 (C-H, adjacent to N of pyridine), 5.1 (C-H, methyl), 7.1-7.8 (C-H, aromatic); m/z: 490.2.

4-(4,5-bis(4-chlorophenyl)-1-(pyridin-2-ylmethyl)-1H-imidazol-2-yl)phenol, 5c Yield: 77%; 1HNMR (δ, ppm): 8.6 (C-H, adjacent to N of pyridine), 5.1 (C-H, methyl), 5.0 (O-H), 7.1-7.8 (C-H, aromatic); m/z: 471.1

2-((4,5-bis(4-chlorophenyl)-2-(4-nitrophenyl)-1H-imidazol-1-yl)methyl)pyridine, 5d Yield: 73%; ^{1}HNMR (δ, ppm): 8.6 (C-H, adjacent to N of pyridine), 8.3 (C-H, adjacent of NO_2), 5.1 (C-H, methyl), 7.1-7.8 (C-H, aromatic); m/z: 501.4.

4-(4,5-bis(4-chlorophenyl)-1-(pyridin-2-ylmethyl)-1H-imidazol-2-yl)-N,N-

dimethylbenzenamine, 5e Yield: 78%; ^{1}HNMR (δ, ppm): 8.6 (C-H, adjacent to N of pyridine), 6.3 (C-H, adjacent to $(NCH_3)_2$), 5.1 (C-H, methyl), 7.1-7.8 (C-H, aromatic), 2.9 (C-H, methylamino); m/z: 499.3.

4-(4,5-bis(4-chlorophenyl)-1-(pyridin-2-ylmethyl)-1H-imidazol-2-yl)-2-methoxyphenol, 5f Yield: 73%; ^{1}HNMR (δ, ppm): 8.6 (C-H, adjacent to N of pyridine), 6.6-6.8 (C-H, adjacent to OCH_3 and OH), 5.1 (C-H, methyl), 5.0 (O-H), 7.1-7.8 (C-H, aromatic), 3.8 (C-H, methoxy); m/z: 502.6.

2-((4,5-bis(4-chlorophenyl)-2-(3,4-dimethoxyphenyl)-1H-imidazol-1-yl)methyl)pyridine, 5g Yield: 76%; ^{1}HNMR (δ, ppm): 8.6 (C-H, adjacent to N of pyridine), 6.6-6.8 (C-H, adjacent to OCH_3), 5.1 (C-H, methyl), 7.1-7.8 (C-H, aromatic), 3.8 (C-H, methoxy); m/z: 516.3.

3-(4,5-bis(4-chlorophenyl)-1-(pyridin-2-ylmethyl)-1H-imidazol-2-yl)phenol, 5 h Yield: 74%; ^{1}HNMR (δ, ppm): 8.6 (C-H, adjacent to N of pyridine), 6.7-7.0 (C-H, adjacent to OH), 5.1 (C-H, methyl), 7.1-7.8 (C-H, aromatic), 5.0 (O-H); m/z: 472.1.

2-(4,5-bis(4-chlorophenyl)-1-(pyridin-2-ylmethyl)-1H-imidazol-2-yl)phenol, 5i Yield: 76%; ^{1}HNMR (δ, ppm): 8.6 (C-H, adjacent to N of pyridine), 6.7-7.0 (C-H, adjacent to OH), 5.1 (C-H, methyl), 7.1-7.8 (C-H, aromatic), 5.0 (O-H); m/z: 472.1.

2-((4,5-bis(4-chlorophenyl)-2-(2-nitrophenyl)-1H-imidazol-1-yl)methyl)pyridine, 5j Yield: 81%; ^{1}HNMR (δ, ppm): 8.6 (C-H, adjacent to N of pyridine), 8.3 (C-H, adjacent of NO_2), 5.1 (C-H, methyl), 7.1-7.8 (C-H, aromatic); m/z: 501.4.

2-((4,5-bis(4-chlorophenyl)-2-(3-nitrophenyl)-1H-imidazol-1-yl)methyl)pyridine, 5k Yield: 77%; ^{1}HNMR (δ, ppm): 8.6 (C-H, adjacent to N of pyridine), 8.3 (C-H, adjacent of NO_2), 5.1 (C-H, methyl), 7.1-7.8 (C-H, aromatic); m/z: 501.4.

2-((4,5-bis(4-chlorophenyl)-2-(4-methoxyphenyl)-1H-imidazol-1-yl)methyl)pyridine, 5l Yield: 79%; ^{1}HNMR (δ, ppm): 8.6 (C-H, adjacent to N of pyridine), 6.6-6.8 (C-H, adjacent to OCH_3), 5.1 (C-H, methyl), 7.1-7.8 (C-H, aromatic), 3.8 (C-H, methoxy); m/z: 486.5.

(E)-2-((4,5-bis(4-chlorophenyl)-2-styryl-1H-imidazol-1-yl)methyl)pyridine, 5m Yield: 79%; ^{1}HNMR (δ, ppm): 8.6 (C-H, adjacent to N of pyridine), 6.9 (C-H, styryl), 7.1-7.8 (C-H, aromatic); m/z: 482.3.

The optimized reaction conditions were able to yield more than 70% of the product, thus making the process efficient for the synthesis of Schiff's bases of imidazoles.

CONCLUSION

Microwave irradiation can lead to efficient heating of molecules by coupling the energy of the microwave with polar molecules. This can help in improving the rate of reaction, reducing the entire reaction time. Optimization of reaction conditions led to a high yield. The microwave conditions when optimized, caused an eco-friendly approach to the synthesis of drugs and molecules. The optimized microwave method for the synthesis of imidazole, revealed 720-watt power and 5.7 min of reaction time and that for the subsequent Schiff bases revealed irradiating at 180-watt power for 111 seconds. The results obtained from the synthesis of Schiff bases were found in consonant with the reaction conditions revealed by the equation.

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Conflict of interest

The authors declare no conflict of interest.

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