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*RESEARCH ARTICLE*

# MICROWAVE ASSISTED SYNTHESIS OF SOME SUBSTITUTED 2-PYRAZOLINE - A GREEN APPROACH.

**[*]Rashmi Sharma[1] and Dr. Ajay M. Chaturvedi[2].**
1. Department of Chemistry, P.M.B. Gujarati Science College, Indore (M.P.).
2. Department of Chemistry, Govt. Madhav Science P.G. College, Ujjain (M.P.).

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## *Abstract*

Microwave assisted synthesis of chalcones under solvent-free conditions resulted in a "green chemistry" procedure for the preparation of 2-pyrazoline derivatives in very good yields. 1-Thiocarbamoyl-3,5-diphenyl-2-pyrazoline was synthesized by the MWI of a mixture of corresponding chalcone, thiosemicarbazide and NaOH in ethanol in modified domestic microwave oven and characterized on the basis of elemental analysis, molecular weight determination and spectral data like $^{1}$H-NMR, IR. These compounds were screened for their antibacterial activity against gram positive and gram negative bacteria.



## Introduction:-

Over the years various innovative methods have been devised to speed up the chemical reactions. In these environmentally conscious days the development of technology is directed towards eco-friendly methods. The usage of microwave energy to accelerate the organic reactions is of increasing interest and offers several advantages over conventional heating techniques.[1] Synthesis of the molecules which normally requires a long time can be achieved conveniently and rapidly in microwave oven. Solvent free condition is especially suitable for microwave activation. Thus the use of microwave energy for the synthesis of organic compounds forms a part of green chemistry.

The partially reduced form of pyrazole is named as pyrazoline or 4,5-dihydropyrazole or 2-pyrazoline. Pyrazolines are nitrogen containing 5-membered heterocyclic compound. It has only one endo-cyclic double bond and is basic in nature[1]. The pyrazoline function is quite stable and has inspired chemists to utilize this stable fragment in bioactive moieties to synthesize new compounds possessing biological activities. Keeping in the view of advantages of microwave heating, in the present investigation we have carried out the synthesis of some α,β-unsaturated ketones (chalcones), which undergo a subsequent cyclization reaction with thiosemicarbazide affording 2-pyrazolines[1]. They have been found to possess antifungal, anticonvulsant, antidepressant, anti-inflammatory, antibacterial, anticancer, antioxidant, antiviral, antiamoebic and antituberculosis activities.[2-16]This reaction is generally carried out in presence of base like NaOH or KOH which are harmful, toxic and polluting. Therefore in the present investigation we have used anhydrous $K_2CO_3$ as the condensing agent which is cheap, non- toxic and easy to use. Furthermore, the reaction can be easily carried out under solvent free condition under microwave irradiation, so as to minimize the pollution. All the prepared compounds were screened for their antimicrobial activities.

**Corresponding Author:- Rashmi Sharma.**
Address:- Department of Chemistry, P.M.B. Gujarati Science College, Indore (M.P.).

**Experimental work:-**

## Material and methods:-

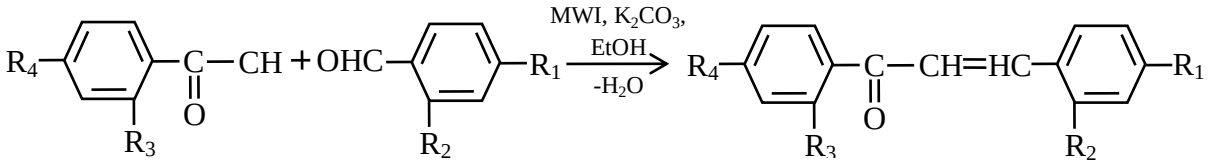
Domestic microwave oven **Electrolux** of 2.54 GHz modified for 'reflux organic synthesis' was used within 100-300 watt level, for MWI method. Microwave safe 'borosil' glass apparatus were used for the synthesis in microwave oven. All the compounds were synthesized by using analytical grade chemicals of Across Organics, Fisher Scientific, Qualigens, CDH and Merck. Melting points of the synthesized compounds are uncorrected and were determined in sealed capillary tubes in **BESTO** melting point apparatus. All the synthesized compounds were characterized by melting point determination, elemental analysis, FTIR, $^1$H-NMR and LCMS spectral studies.

**Synthesis of Substituted Pyrazolines:-**

Substituted pyrazoline was synthesized in two steps by MWI method. The general method for the synthesis of substituted pyrazoline is as follows:

**Step I: Synthesis of substituted chalcones:-**

In the first step an equimolar quantity of various substituted acetophenones and substituted aromatic aldehydes were thoroughly mixed with anhydrous $K_2CO_3$ to form a thick paste. The paste was air dried and the residual mass was subjected to microwave irradiation for 3-5 minutes. After completion of the reaction the contents were dissolved in ethanol. Inorganic material was filtered off and filtrate after concentration in vacuum was left overnight to afford the desired chalcones in 80-90% yield.[17-22] The analytical and physical data of the synthesized compounds **(1a, 1b, 1d, 1e)** is summarized in **Table -1**

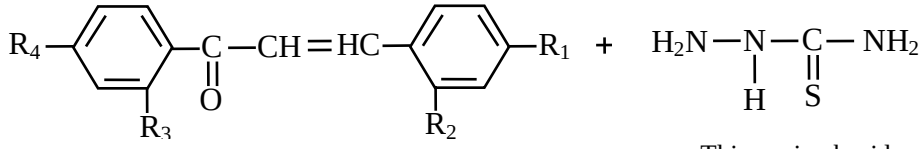



**Substituted Acetophenone** **Substituted Benzaldehyde** **Substituted Chalcone**

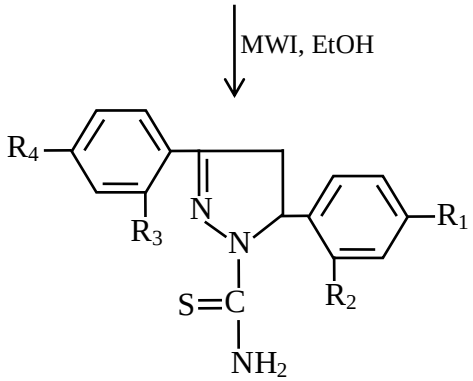
**Scheme - I**

**Step II: Synthesis of substituted pyrazolines:-**

In the second step, synthesized chalcones were treated with thiosemicarbazide, and various substituted pyrazolines were synthesized. All the reagents were taken in equimolar ratio (0.01mole) in ethanol and their mixture solution was microwave irradiated for 10-15 minutes cautiously at low temperature in modified microwave oven.[23-25] The analytical and physical data of the synthesized compound **(2a, 2b, 2d, 2e)** is summarized in **Table - 2**



Substituted Chalcone Thiosemicarbazide




1-Thiocarbamoyl-3,5-diphenyl-2-pyrazoline

Where, $R_1$, $R_2$, $R_3$, $R_4$ = -H, OH, $-OCH_3$, -Cl or $-NO_2$ in different ligands.

**Scheme - II**

**Experimental Data of Compounds:-**

**Table-1:-** Analytical and Physical data of synthesized Chalcones:

| Product | Molecular formula | Molecular weight in g/mol | Colour | M.P. (°C) | Yield (%) | Time required (min.) |
|---|---|---|---|---|---|---|
| **1a** | $C_{15}H_{12}O$ | 208.25 | Yellow | 56 | 82 | 4-6 |
| **1b** | $C_{15}H_{11}ClO_2$ | 257.50 | Yellow | 131 | 90 | 4-6 |
| **1d** | $C_{15}H_{10}Cl_2O$ | 277.14 | Pale Yellow | 110 | 90 | 4-6 |
| **1e** | $C_{16}H_{14}O_3$ | 254.00 | Yellow | 169 | 92 | 4-6 |

**Table-2:-** Analytical and Physical data of synthesized Pyrazolines

| Product | Molecular formula | M.W. Found (calculated) in g/mol | Colour | M.P. (°C) | Yield (%) | Elemental analysis found (calculated) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | %C | %H | %N | %S | %Cl |
| **2a** | $C_{16}H_{15}SN_3$ | 281.37 (280.3) | Pale yellow | 165 | 55 | 68.3 (68.6) | 5.37 (5.8) | 14.93 (15.2) | 11.4 (11.8) | - |
| **2b** | $C_{16}H_{14}SN_3ClO$ | 313.81 (312.6) | Yellow | 226 | 89 | 57.91 (58.1) | 4.25 (4.6) | 12.66 (12.7) | 9.66 (10.2) | 10.68 (10.8) |
| **2d** | $C_{16}H_{13}SN_3Cl_2$ | 350.26 (349.2) | Yellow | 142 | 68 | 54.86 (54.9) | 3.74 (3.9) | 12.0 (12.8) | 9.15 (9.4) | 20.24 (20.6) |
| **2e** | $C_{17}H_{17}SN_3O_2$ | 327.40 (326.6) | Creamy yellow | 227 | 51 | 62.36 (62.5) | 5.23 (5.4) | 12.83 (12.9) | 9.79 (10.2) | - |

**Spectral Data of Compounds:-**

**(2a) 1-Thiocarbamoyl-3,5-diphenyl-2-pyrazoline:**

IR $\upsilon(cm^{-1})$: 1582(C=N), 1071(C-N), 827 (N-N), 1564 & 3000-3042 (Ar-nu), 1147(C=S); $^1$H-NMR δ(ppm): 3.3-3.1($C_4$-$CH_2$), 4.0 ($C_5$-CH),7.7-6.6 (Ar-H).

**(2b) 1-Thiocarbamoyl-3-(2'-hydroxyphenyl)-5-(4-chlorophenyl)-2-pyrazoline:**

IR $\upsilon(cm^{-1})$: 1584(C=N), 1073(C-N), 825(N-N),1590 & 3000-3045(Ar-nu), 1170 (C=S), 3080-2990 (Ar-OH); $^1$H-NMR δ(ppm): 3.3-2.9($C_4$-$CH_2$), 6.3($C_5$-CH), 7.4-6.3(Ar-H), 7.4(Ar-OH).

**(2d) 1-Thiocarbamoyl-3-(4'-chlorophenyl)-5-(4-chlorophenyl)-2-pyrazoline:**

IR $\upsilon(cm^{-1})$: 1578(C=N),1082(C-N), 814(N-N), 1599 & 2995-3070(Ar-nu), 1183(C=S), 773(C-Cl); $^1$H-NMR δ(ppm): 3.4-2.5 ($C_4$-$CH_2$), 6.1($C_5$-CH), 8.1-7.2(Ar-H).

**(2e) 1-Thiocarbamoyl-3-(4'-hydroxyphenyl)-5-(4-methoxyphenyl)-2-pyrazoline:**

IR $\upsilon(cm^{-1})$: 1586(C=N),1076(C-N), 813(N-N), 1603 & 3025-3074(Ar-nu), 449(C=S), 3095-2990(Ar-OH); $^1$H-NMR δ(ppm): 3.5-2.9($C_4$-$CH_2$), 5.9($C_5$-CH),8.3-7.5 (Ar-H), 10.9-9.8 (Ar-OH).

**Antimicrobial Activity:-**

The biocidal activity of synthesized substituted pyrazolines was studied in order to prove their utility. For this purpose, some bacteria's like Staphylococcus aureus MRSA (gram positive bacteria), Pseudomonas spp. (gram positive bacteria), Escherichia coli (gram negative bacteria), Bacillus cereus (gram negative bacteria) were cultured on Mueller- Hinton agar plates and by using block well diffusion method, then the effect of synthesized pyrazolines **(2a, 2b, 2c, and 2d)** were screened. All the synthesized compounds exhibited moderate to excellent antibacterial activities. Some of them were found to be more effective in comparison to standard drugs (Amikacin and Gentamicin). Antimicrobial activity of the synthesized compounds is represented in **Table 3.**

**Table 3:-** Antimicrobial activity of substituted 1-Thiocarbamoyl-3,5-diphenyl-2-pyrazoline

| Compound | Zone of Inhibition in mm | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Bacteria | | | | | | | |
| | S. Aureus | | E. Coli | | Pseudomonas | | Bacillus | |
| | Zone size | Activity | Zone size | Activity | Zone size | Activity | Zone size | Activity |
| 2a | 05 | R | 11 | I | 06 | R | 06 | R |
| 2b | 13 | I | 22 | E | 08 | R | 11 | I |
| 2d | 08 | R | 06 | R | 20 | E | 08 | R |
| 2e | 20 | E | 13 | I | 14 | I | 20 | E |
| Std. Drug (Amk and Gen) | 05<br>06 | R<br>R | 12<br>12 | I<br>I | 12<br>14 | I<br>I | 16<br>18 | S<br>S |

## Results and Discussion:-

In this paper, microwave assisted synthesis of chalcones **(1a**, **1b, 1d** and **1e)** has been reported by the reaction of substituted acetophenone and substituted benzaldehydes in the presence of anhydrous $K_2CO_3$. These chalcones were treated with thiosemicarbazide under microwave irradiation to yield 2-pyrazolines **(2a**, **2b, 2d** and **2e),** in 10-15 minutes. The synthetic procedure for preparation of title compounds is given in reaction scheme I and II. The assigned structure and molecular formula of the newly synthesized compounds **(2a**, **2b, 2d** and **2e)** were confirmed and supported by $^1$H- NMR and IR data as well as elemental analysis, which was in full agreement with proposed structures. All the compounds were screened in vitro for their antibacterial potential by block well diffusion assay against selected bacteria. The results of antibacterial activities expressed in terms of zone of inhibition are reported in **Table 3**. All the synthesized compounds have shown significant to excellent activity against *E. coli*, *S. aureaus*, *Bacillus* and *Pseudomonas*.

## Conclusion:-

In summary, this work demonstrates a rapid, efficient and environment friendly method for the synthesis of these compounds (substituted chalcones and 2-pyrazolines) under microwave irradiation. The results obtained confirm that the use of microwave has shown the advantages like high yields, relatively short reaction times, low cost, simple experimental and isolation procedures, and finally, it is in agreement with the green chemistry protocols. The results of antimicrobial studies of synthesized compounds revealed that they possess moderate to potent antibacterial activities against the tested gram positive and gram negative microorganisms. The data reported in this paper may be helpful as a guide for the medicinal chemists, who are working in this area.

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