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# Ultrasonic and Microwave Accelerated Vilsmeier-Haack Formylation: An Energy-efficient Route to Synthesize Pyrazole-4-Carbaldehydes.

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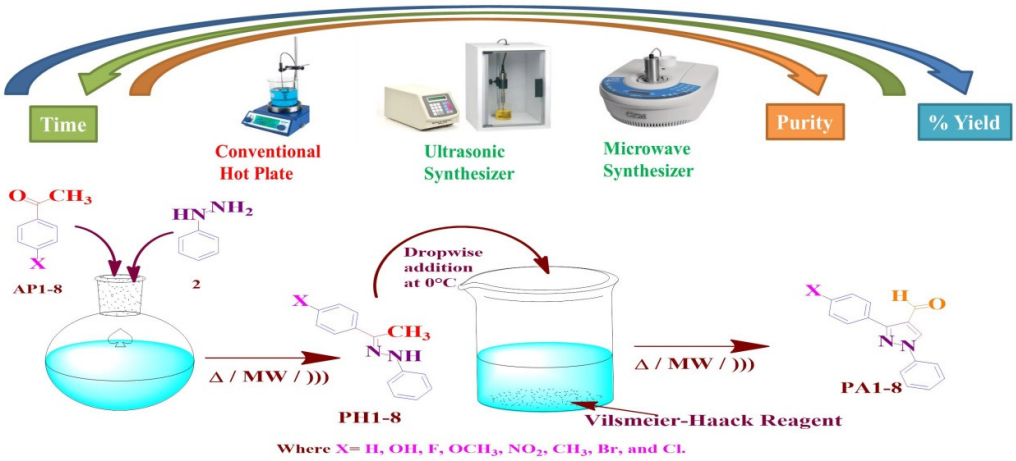
**ABSTRACT:**

Due to the long reaction time and toxic waste intermediate formation from the most used classic thermal Vilsmeier–Haack (VH) reaction, created a need for the advancement of a more proficient way for the synthesis of pyrazole-4-carbaldehydes. A facile, environmentally benign synthetic protocol was set to reduce the by-product. We used microwave and ultrasound (sonication) as cost-effective and energy-efficient sources for our synthesis. We have successfully used dipolar aprotic green solvent ethanol and acetonitrile, in a synthetic procedure of Pyrazole formylation to avoid reproductive toxicity of traditionally used solvent. A series of 1-phenyl-3-(p-substituted phenyl)-1H-pyrazole-4-carbaldehydes PA (1-8) were synthesized from substituted phenylhydrazones and VH reagent. Longer reaction times (1-7 hours) under the normal conditions reduced to 10-60 min under sonication, while microwave assisted reactions further reduced the reaction time to only 5-15 minutes. The newly synthesized derivatives were elucidated using FT-IR, 1H-NMR, and mass spectroscopy. This approach provides numerous advantages over conventional practices, comprising reduced energy waste, smaller reaction times, higher yields, and easier work-up process.

**GRAPHICAL ABSTRACT:**




**A Greener Route to Synthesize Pyrazole-4-carbaldehydes through Vilsmeier-Haack formylation.**

**KEYWORDS:** MICROWAVES, ULTRASOUND, GREEN CHEMISTRY, PYRAZOLE ALDEHYDE, VILSMEIER-HAACK.

**INTRODUCTION:**

The development of simple, mild, practicable, cheap, and benign methods for the synthesis of heterocycles has become the primary goal of today's researchers. Green chemistry addresses many components of synthetic reactions. One of the important components is the nonconventional energy source required to drive a reaction to completion. Though a "room temperature" reaction is considered to be an idle "green" reaction, there are many reactions that are reluctant to advance without the application of external energy, i. e. high-temperature reactions. In these cases, conventional heating poses many problems such as long reaction time leading to waste of energy and often unnecessary by-product formation. In such cases, the reactions can be made benign by using alternative energy sources like microwave heating, ultrasonic sound, and ultraviolet/visible light.[1]

Pyrazoles, a key component of the heterocyclic family, have received a lot of attention in medicinal chemistry due to their important biological properties.[2] Pyrazole-4-carbaldehyde employed a prominent place because they are valuable precursors for several synthetically useful building blocks such as chalcones, amides, hydrazides, alcohols, Schiff bases, esters, nitriles, amines, carboxylic acids, and numerous organic as well as heterocyclic compounds. [3,4] However, several derivatives of pyrazole-4-carbaldehyde shown anticancer, antiparasitic, and antibacterial properties.[5] Additionally, pyrazoles can be formylated at the 4-position of the heteroaromatic ring using a variety of techniques.[6, 7]

Due to the long reaction time and toxic waste intermediate formation from the most used classic thermal Vilsmeier–Haack (VH) reaction, created a need for the advancement of a more proficient way for the synthesis of pyrazole-4-carbaldehydes.

The microwave-assisted organic synthesis (MAOS) is gaining popularity as an unconventional heating method since it drastically shortens reaction times. Owing to this benefit, microwaves are increasingly being used to establish more sustainable synthetic protocols for drug and fine chemical synthesis. The adoption of such promising strategies in conjunction with the greener reaction medium is drastically decreasing chemical waste and reaction times in various organic syntheses and chemical transformations.[8,9] As microwave heating speeds up reactions, increases yields, and shortens reaction periods, it has been used in numerous organic transformations. The distinct thermal and non-thermal impacts are the cause of all these effects. Overheating, selective heating, and hot spots account for the thermal effect, whereas the highly polarizing field and more effective contacts account for the non-thermal effect.[10]

Ultrasound-enhanced synthesis is considered a green chemical approach since it uses milder reaction conditions, shorter reaction times, high efficiency, and minimal energy requirements. Sonochemistry's distinctive feature is its cavitation phenomenon. Cavitation is a physical process that generates, expands, and degrades gaseous bubbles in an irradiated liquid. Cavitation generates extremely high local temperatures and pressures within the bubbles, resulting in turbulent liquid flow and improved mass transfer. [11,12]

In the present work, we adopted the eco-friendly energy sources for sustainable synthesis of 1-phenyl-3-(p-substituted phenyl)-1Hpyrazole-4-carbaldehydes 2a-d. Shorter reaction time, by-product elimination, improved yields, enhanced selectivity, and homogeneous heating are the major advantages offered by the ultrasound and microwave irradiation methods in relation to conventional thermal reactions.

**RESULTS AND DISCUSSION:**

The protocol espoused for the synthesis of compounds 1-phenyl-3-(p-substituted phenyl)-1Hpyrazole-4-carbaldehydes PA (1-8) is outlined in Scheme 1. Compounds PA (1-8) were synthesized in two steps. The hydrazones PH (1-8) were initially prepared from ketones AP (1-8) and phenyl-hydrazine, which on additional reaction with VHR (DMF/$POCl_3$) undergoes cyclization to give pyrazole 4-carbaldehydes. Although the use of POCl3/DMF adducts was well acknowledged for the cyclization of hydrazones of keto compounds, the hunting for innovative techniques for translation of hydrazones into 4-formylpyrazoles is still in advancement.

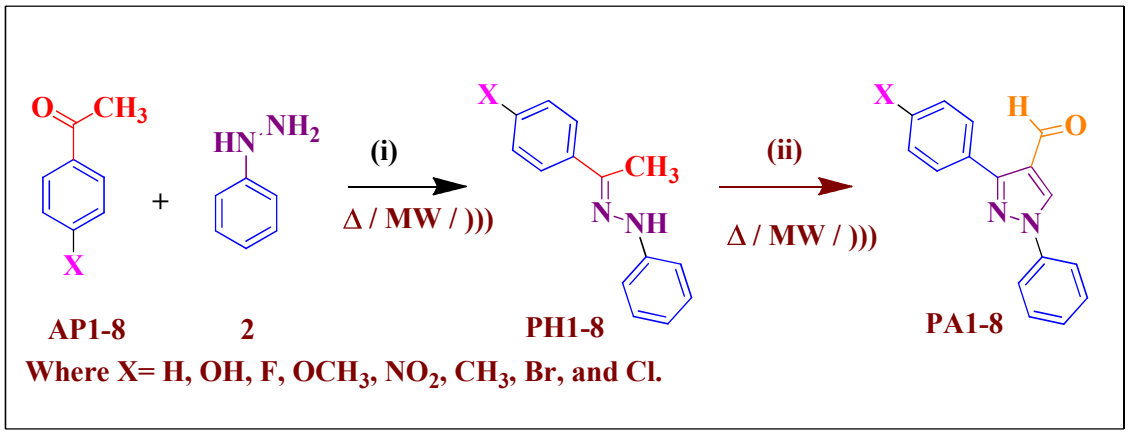



**Figure 1** General synthesis of compound PA1-8. Reagents and conditions: (i) acetic acid, ethanol, warm, 1-4 h (ii) $POCl_3$ & DMF at 0°C, 2-5 h, and neutralized through $K_2CO_3$.

To explore the general scope and versatility of VH formylation reaction conditions to improve the yield and decrease the time, the reaction has been carried out under conventional heating, sonication, and microwave irradiation methods. A sample reaction was conducted by using 1-(1-(4- -phenyl)-ethylidene)-2-phenyl-hydrazine with VHR for the synthesis of compound PA3 to check the effect of microwave irradiation. An optimization study was carried out by varying the solvent, temperature, and power ratings.

An initial exploration of the solvent impact on the synthesis of compound PA3 has been conveyed by using different solvents as shown in Table 1. The rate of PA3 formation was observed to be increased with the use of high dielectric constant and high boiling solvent DMF, thereafter in MeCN. Both solvents were found to be the best solvent in the microwave irradiation method with relatively higher yield, because of their higher dielectric loss value (6.07 & 2.32) and Tan δ value (0.161 & 0.062) successively among the solvents used in this study. We have successfully replaced DMF, with dipolar aprotic green solvent acetonitrile, in a synthesis procedure of Pyrazole formylation to avoid reproductive toxicity due to DMF. In spite of knowing toxicity of DMF its use in the preparation of VH reagent is unavoidable. VH was prepared at 0°C and was added to the reaction mixture at same temperature, may reduce its toxicity.

**Table 1 Optimization of reactions solvent condition on the yield of compound PA3**

| Entry | Solvent | Yield (%) | |
|---|---|---|---|
| | | Conventional | MW method |
| 1 | DCM | 18 | 34 |
| 2 | DMF | 67 | 85 |
| 3 | MeCN | 48 | 81 |
| 4 | THF | 16 | 27 |
| 5 | DME | 23 | 31 |

The microwave method proved to be effective, allowing the synthesis of the target product PA2 in 85% high yield within 10 minutes, resulting in a 25% increase in yield at 60°C (entry 5, Table 2). A steady increase in yield was seen at 40°C, corresponding with a rise in power from 100 to 300 W. However, at 60°C and 80°C, a minor depletion in yield was noted at higher power levels of 300W. The best yield was obtained at 60°C with a power rating of 200 W, as 100 W did not offer a suitable threshold. Nevertheless, at 300 W, supercritical solvent heating may be the cause of the breakdown of VHR, leading to a significant decrease in yield (56% and 63% respectively, entries 9 and 6, Table 1).

**Table 2.** Optimisation of MAOS reaction parameters for the synthesis of compound PA3.

| | Reaction Parameter | | | |
|---|---|---|---|---|
| Entry | Temp. (°C) | Power rating (W) | Time (min) | Yield (%) |
| 1 | 40 | 100 | 10 | 27 |
| 2 | 40 | 200 | 10 | 48 |
| 3 | 40 | 300 | 10 | 52 |
| 4 | 60 | 100 | 10 | 58 |
| 5 | 60 | 200 | 10 | 85 |
| 6 | 60 | 300 | 10 | 63 |
| 7 | 80 | 100 | 10 | 51 |
| 8 | 80 | 200 | 10 | 68 |
| 9 | 80 | 300 | 10 | 56 |

To determine the optimal Ultrasonic irradiation parameters for hydrazone cyclization in the presence of VHR, the effect of temperature and time on the synthesis of sample compound PA3 was investigated (Table 3). We carried out the same synthesis with optimum ultrasonic irradiation at 20 kHz at three distinct temperatures: 40, 60, and 80°C. We discovered that the reaction does not proceed properly and the yield is significantly lower at 40°C. However, yields at 80°C are somewhat lower than those at 60°C. The higher temperature may decompose the VHR to some extent. The greater temperature may partially break down the VHR. At this temperature, cavitation increases, improving the responsiveness of the various substrates.

**Table 3.** Optimisation of Ultrasonic reaction parameters for the synthesis of compound PA3.

| | **Reaction Parameter** | | |
|---|---|---|---|
| **Entry** | **Temp. (°C)** | **Time (min)** | **Yield (%)** |
| 1 | 40 | 85 | 68 |
| 2 | 60 | 60 | 81 |
| 3 | 80 | 50 | 73 |

We described a series of 3-(4-substituted-phenyl)-1-phenyl-1H-pyrazole-4-carbaldehydes PA (1-8) that were optimized under ultrasonically and microwave-assisted conditions. The findings are summarized in Table 4. The yields that were reported were found to be very substituent-dependent and generally satisfactory. This suggests a number of important benefits, such as increased yields, purity, and faster reaction speeds. The primary benefit of using MW and ultrasonic in conjunction with conventional procedures is the notable reduction in reaction times and the creation of more comfortable experimental settings when compared to the traditional heating approach.

**Table 4** Comparison of reaction time and yields of the synthesized compounds (PH1-PH8) and (PA1-PA8) under different conditions.

| **Compound** | **R** | **Conventional Method** | | **Sonication Method** | | **Microwave** | |
|---|---|---|---|---|---|---|---|
| | | **Time (h)** | **Yield (%)** | **Time (min)** | **Yield (%)** | **Time (min)** | **Yield (%)** |
| PH1 | H | 1 | 85 | 10 | 89 | 05 | 90 |
| PH2 | OH | 3 | 82 | 20 | 90 | 15 | 93 |
| PH3 | F | 4 | 78 | 25 | 81 | 10 | 85 |
| PH4 | $OCH_3$ | 2 | 57 | 15 | 63 | 05 | 76 |
| PH5 | $NO_2$ | 4 | 73 | 15 | 79 | 10 | 88 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| PH6 | $CH_3$ | 5 | 68 | 25 | 71 | 15 | 76 |
| PH7 | Br | 4 | 74 | 20 | 81 | 10 | 84 |
| PH8 | Cl | 4 | 75 | 20 | 86 | 10 | 89 |
| PA1 | H | 2 | 63 | 15 | 87 | 10 | 94 |
| PA2 | OH | 6 | 65 | 50 | 77 | 15 | 86 |
| PA3 | F | 5 | 64 | 60 | 78 | 15 | 85 |
| PA4 | $OCH_3$ | 2 | 59 | 35 | 72 | 10 | 87 |
| PA5 | $NO_2$ | 3 | 76 | 45 | 89 | 10 | 96 |
| PA6 | $CH_3$ | 4 | 69 | 60 | 82 | 15 | 84 |
| PA7 | Br | 4 | 67 | 50 | 73 | 10 | 85 |
| PA8 | Cl | 5 | 64 | 55 | 76 | 15 | 89 |

Under sonication, reaction times decreased from 2–6 hours to 10–60 minutes, and under microwave assistance, they only took 5–15 minutes. Thus, the experimental findings in this work may be explained by acoustic cavitation effects. However, in addition to the direct absorption of the selected microwave energy by the reactive species, whether polar or dipolar, microwave irradiation results in increased dipole-dipole and ionic interactions.

The IR spectra of the synthesized substituted pyrazole-4-carbaldehydes (PA-1-PA8) were confirmed from the arrival of carbonyl (C=O) band ranging from 1666 to 1730 $cm^{-1}$ along with characteristic C─H stretching from 2780 to 2924 $cm^{-1}$. Whereas, amine (N–H) stretching bands ranging between (3370 and 3300 $cm^{-1}$) confirmed substituted hydrazones (PH1-PH8) vanished from aldehyde spectra. The singlet of $^{1}H$ NMR appeared in the range of (10.11 to 9.53 δ) and (9.03 to 8.3 δ) confirming the presence of –CHO function and pyrazole ring formation. Furthermore, the appearance of the highest δ peak in $^{13}C$ NMR between (191.5 to 193.7) confirmed the formation of 4-formyl pyrazoles from hydrazones.

## EXPERIMENTAL:

### Materials and Methods:

Reagents and solvents were purchased from Merck Life Science Pvt Ltd, Finar Limited, Sigma-Aldrich, and Avra Synthesis Private Ltd. For synthetic work, a) Ultra-sonication was performed with a Vibracell VCX-500 (500W, 220V, and 20 kHz) (Sonics Instruments, USA) equipped with a solid synthesis probe of titanium tip (13 mm diameter). b) Microwave-assisted experiments were carried out in a CEM Discover microwave synthesizer. Reactions were monitored by TLC on precoated aluminum plates from Merck (Silica gel 60 F254); spots were visualized under UV light at 254nm or in an iodine chamber. Finar 200–400 mesh silica was used for column chromatography. Flash

chromatography was performed on automated Yamazen Flash Chromatography. Melting points were concluded (uncorrected) by operating OptiMelt MPA100 melting point equipment. IR spectra were recorded on Bruker Alpha E FTIR spectrophotometer. Characterization data have shown a good correlation with literature values and mass, $^{1}H$ NMR and $^{13}C$ NMR numbers of the compound were reported from the literature.

**General procedure for 1-(1-(4-subtituted-phenyl)-ethylidene)-2-phenylhydrazine** PH1-PH8 **synthesis.**

**Conventional method**

Warm and stir a mixture of 40 mmol of para-substituted acetophenone (AP1- AP8) and 40 mmol of phenylhydrazine in 20 ml of anhydrous ethanol. Add a few drops of glacial acetic acid and reflux the mixture for 1-4 h. Cool the flask, solid will appear, filter and wash the solid with dil. HCl followed by about 10 ml of cold rectified spirit. Pure product was obtained by recrystallization in ethanol and dried in a vacuum over $P_2O_5$.[13]

**Microwave irradiation method**

A mixture of phenyl-hydrazine (40 mmol), para-substituted acetophenone (AP1- AP8) (40 mmol), and ethanol (5 mL) in glacial acetic acid (2 drops) was exposed to microwave irradiation at 200 W for 5–15 min with 5–10 s intervals and the advancement of the reaction was supervised by TLC. The reaction mixture was poured into crushed ice. The gained solid was filtered, washed with water, dried, and purified by recrystallization from ethanol to give (PH1-PH8).

**Ultrasonic irradiation method**

In a 50 mL beaker, a mixture of phenyl-hydrazine (40 mmol), para-substituted acetophenone (AP1- AP8) (40 mmol), and ethanol (25 mL) in glacial acetic acid (2 drops) was irradiated using the ultrasonic probe at the frequencies of 20 kHz at the required temperature for reaction time [Table 4]. The acquired solid was filtered, washed with cold water, dried, and purified by recrystallization from ethanol to give title products.

**1-phenyl-2-(1-phenylethylidene)-hydrazine(PH1):**

Yield 89.93 %; grey white crystaline Solid; M.P. 104-106 °C; $^{1}H$ NMR (400 MHz, CDCl3, TMS, ppm): δ= 9.72 (s; 1H, NH), 7.81 (dd; *J*=8.18, Hz; 2H), 7.69 (dd; *J*=7.83Hz; 2H), 7.66 (dd; *J*=8.39 Hz; 1H), 7.69 (dd; *J*=7.77 Hz; 1H), 7.55 (d, *J*=8.7 Hz; 2H), 6.96 (dd; *J*=8.19 Hz; 2H), 2.49 (s; 3H), $^{13}C$ NMR (400 MHz, $CDCl_3$, δ, ppm): 16.7 ($CH_3$), 114.3, 124.2, 128.3, 129.8, 131.4, 138.1, 144.8, 165.3; FTIR-ATR: 3314 (s) (N-H); 1608 (s) (C=N); MS (m/z): $[M^+2H]^+$ calculated for $C_{14}H_{14}N_2$ 210.27, obtained 211.35. Anal. Calc. for $C_{14}H_{14}N_2$: C, 79.97; H, 6.71; N, 13.32. Found: C, 80.06; H, 6.69; N, 13.61 %.[14,15,16,17]

**4-(1-(2-phenylhydrazono)-ethyl)-phenol (PH2):**

Yield 93 %; white Solid; M.P. 146-148 °C; $^{1}H$ NMR (600 MHz, DMSO-$d_6$, TMS, ppm): δ= 9.55 (s; 1H, OH), 9.03 (s; 1H, NH), 7.63 (d; *J*=8.11, Hz; 2H), 7.19 (d; *J*=6.3 Hz; 4H), 6.78 (d; *J*= 6.7 Hz; 2H), 6.72 (dd; *J*= 7.33 Hz; 1H), 2.19 (s; 3H, $CH_3$); FTIR-ATR: 3447 (O-H), 3370 (N-H); 2933, 2860 (C-H), 1598 (C=N) 1177 (C-O); MS (m/z): $[M^+2H]^+$

calculated for $C_{14}H_{14}N_2O$ 226.27, obtained 227.30. Anal. Calc. for $C_{14}H_{14}N_2O$: C, 74.31; H, 6.24; N, 12.38; O, 7.07. Found: C, 74.28; H, 6.08; N, 11.17 %.[18,19]

**1-(1-(4-fluorophenyl)ethylidene)-2-phenylhydrazine (PH3):**

Yield 82 %; Light yellow Solid; M.P. 134-136 °C; $^1$H NMR (300 MHz, DMSO-$d_6$, TMS, ppm): δ= 7.91 (dd; *J*=8.18, Hz; 2H), 7.69 (dd; *J*=7.83Hz; 2H), 7.66 (dd; *J*=8.39 Hz; 1H), 7.55 (d, *J*=8.7 Hz; 2H), 7.37 (dd; *J*=8.19 Hz; 2H), 6.76 (s; 1H), 2.28 (s; 3H); $^{13}$C NMR (100 MHz, DMSO-$d_6$, δ, ppm): 17.8 ($CH_3$), 113.7–145.3 (Ar–C), 163.1 (C–F), 167.3 (–C55N); $^{19}$F NMR (282 MHz, DMSO-$d_6$, δ, ppm): 118.37 (s, 1F, 4-F); FTIR-ATR: 3354 (s) (N-H); 3024 (s) (C-H), 1431 (C-H); MS (m/z): $[M^+2H]^+$ calculated for $C_{14}H_{13}FN_2$ 228.26, obtained 229.31. Anal. Calc. for $C_{14}H_{13}FN_2$: C, 73.66; H, 5.74; F, 8.32; N, 12.27. Found: C, 73.60; H, 5.79; N, 12.36 %, Rf= 0.52 ($SiO_2$, n-hexane/ethyl acetate,v/v, 3 : 1).[20]

**1-(1-(4-methoxyphenyl)ethylidene)-2-phenylhydrazine (PH4):**

Yield 57 %; White Solid; M.P. 108-110°C; $^1$H NMR (400 MHz, $CDCl_3$, TMS, ppm): δ= 9.76 (s; 1H, NH), 7.75 (dd; *J*= 7.3, Hz; 2H), 7.37 (dd; *J*= 7.6 Hz; 2H), 7.28 (dd; *J*= 8.2 Hz; 1H), 6.91 (d, *J*= 8.3 Hz; 2H), 7.37 (dd; *J*= 7.2 Hz; 2H), 3.44 (s; 3H, $OCH_3$), 2.51 (s; 3H, $CH_3$); $^{13}$C NMR (400 MHz, $CDCl_3$, δ, ppm): 17.74 ($CH_3$), 115.1, 124.5, 128.8, 131.4, 131.7, 139.3, 145.2, 161.4, 165.9; FTIR (KBr, $cm^{-1}$): 3315 (N-H str.); 3054 (s) (C-H), 1604 (C=N), 1500 and 1441 (Ar C=C str.), 1250 (C-N st.), 1028 (C-O str.); MS (m/z): $[M^+2H]^+$ calculated for $C_{15}H_{16}N_2O$ 240.30, obtained 241.54. Anal. Calc. for $C_{15}H_{16}N_2O$: C, 74.97; H, 6.71; N, 11.66. Found: C, 75.23; H, 6.73; N, 12.09 %.[21]

**1-(1-(4-nitrophenyl)ethylidene)-2-phenylhydrazine (PH5):**

Yield 88 %; Red Solid; M.P. 145-148°C; $^1$H NMR (300 MHz, DMSO-$d_6$, TMS, ppm): δ= 7.84 (dd; *J*=8.24, Hz; 2H), 7.79 (dd; *J*=7.6 Hz; 2H), 7.46 (dd; *J*=5.19 Hz; 1H), 7.36 (d, *J*=8.7 Hz; 2H), 7.21 (d; *J*=9.2 Hz; 2H), 6.68 (s; 1H), 2.32 (s; 3H); $^{13}$C NMR (100 MHz, DMSO-$d_6$, δ, ppm): 146.74, 144.70, 142.80, 133.82, 129.21, 126.09, 123.90, 120.28, 112.78, 15.91; FTIR-ATR $cm^{-1}$: 3300 (s) (N-H); 1597 (C=N), 1550 (N=O); MS (m/z): $[M^+2H]^+$ calculated for $C_{14}H_{13}N_3O_2$ 255.27, obtained 256.08. Anal. Calc. for $C_{14}H_{13}N_3O_2$: C, 65.87; H, 5.13; N, 16.46; O, 12.54. Found: C, 65.83; H, 4.89; N, 16.38 %.[22,23]

**1-phenyl-2-(1-(p-tolyl)ethylidene)hydrazine (PH6):**

Yield 76 %; Yellow Solid; M.P. 106-108°C; $^1$H NMR (300 MHz, DMSO-$d_6$, TMS, ppm): δ= 7.82 (dd; *J*=8.21, Hz; 2H), 7.76 (dd; *J*= 7.16 Hz; 2H), 7.41 (dd; *J*=5.24 Hz; 1H), 7.35 (d, *J*=8.66 Hz; 2H), 7.22 (d; *J*=9.3 Hz; 2H), 6.64 (s; 1H), 2.36 (s; 3H); FTIR-ATR: 3352 (s) (N-H); 3054 (s) (C-H), 1451 (C-H); MS (m/z): $[M^+2H]^+$ calculated for $C_{15}H_{16}N_2$ 224.30, obtained 225.13. Anal. Calc. for $C_{15}H_{16}N_2$: C, 80.32; H, 7.19; N, 12.49. Found: C, 80.28; H, 6.89; N, 12.37 %.

**1-(1-(4-bromophenyl)ethylidene)-2-phenylhydrazine (PH7):**

Yield 84 %; Yellow Solid; M.P. 132-134°C; $^1$H NMR (300 MHz, $CDCl_3$, TMS, ppm): δ= 8.25 (dd; *J*=8.22, Hz; 2H), 8.19 (dd; *J*=7.16 Hz; 2H), 7.68 (dd; *J*=5.9 Hz; 1H), 7.42 (d, *J*= 8.37 Hz; 2H), 7.15 (d; *J*= 8.24 Hz; 2H), 5.25 (s; 1H, NH), 3.32 (s; 3H, $CH_3$); FTIR-ATR: 3354 (s) (N-H); 3095 (s) (C-H), 1627 (C=N), 1525 (N-N); MS (m/z): $[M^+2H]^+$ calculated for $C_{14}H_{13}BrN_2$ 289.17, obtained 290.02. Anal. Calc. for $C_{14}H_{13}BrN_2$: C, 58.15; H, 4.53; Br, 27.63; N, 9.69. Found: C, 57.95; H, 4.46; Br, 27.54; N, 9.62 %.[24]

**1-(1-(4-chlorophenyl)ethylidene)-2-phenylhydrazine (PH8):**

Recrystallized from ethyl acetate; Yield 89 %; Yellow Solid; M.P. 102-104°C; $^1$H NMR (300 MHz, DMSO-$d_6$, TMS, ppm): δ= 7.84 (dd; *J*=8.24, Hz; 2H), 7.79 (dd; *J*=7.6 Hz; 2H), 7.46 (dd; *J*=5.19 Hz; 1H), 7.36 (d, *J*=8.7 Hz; 2H), 7.21 (d; *J*=9.2 Hz; 2H), 6.68 (s; 1H), 2.32 (s; 3H); FTIR-ATR: 3304 (s) (N-H); 3084 (s) (C-H), 1531 (C-H); MS (m/z): $[M^+2H]^+$ calculated for $C_{14}H_{13}ClN_2$ 244.72, obtained 245.08. Anal. Calc. for $C_{14}H_{13}ClN_2$: C, 68.71; H, 5.35; Cl, 14.49; N, 11.45. Found: C, 68.79; H, 5.27; Cl, 14.42; N, 11.38 %.[25]

**General procedure for synthesis of 1, 3-diarylpyrazole aldehyde. (PA1-PA8)**

**Conventional method**

VHR was prepared by drop-wise addition of $POCl_3$ (30 mmol) in DMF (30 mmol) and was previously separately cooled at 0°C before being stirred over a period of 30 min. A solution of p-substituted-acetophenone phenylhydrazone (AP1- AP8) (10 mmol) in acetonitrile (MeCN) (3 mL) was added dropwise to the reaction mixture at 0°C. The reaction mixture was kept at r.t. for 30 min and then heated at 60–80 °C for 2-8 h until the precipitate was obtained. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was then cooled to r.t. and poured into crushed ice with stirring and neutralized with a cool saturated aq. $K_2CO_3$ solution. The precipitate was filtered, strongly washed with water and recrystallized from ethanol. 1, 3-diarylpyrazole aldehydes have been synthesized according to the method reported in the literature.[26]

**Microwave irradiation method**

To a freshly prepared VHR, obtained by following the above-mentioned conventional procedure. A solution of p-substituted-acetophenone phenylhydrazone (AP1- AP8) (10 mmol) in MeCN (3 mL) was added dropwise to the reaction mixture at 0°C. After completion of the addition, the reaction flask was kept at r.t. for 30 min. The reaction flask was then subjected to microwave irradiation and the temperature was ramped from room temperature to 60°C with a holding time of 5-15 minutes. The oven was set at 200 W for 5 s with 6–10 min intervals until the precipitate was obtained. The progress of the reaction was monitored by TLC (eluent: DCM: ethyl acetate 8:2). Then the reaction was brought to r.t., quenched with crushed ice, and neutralized with a cool saturated aq. $K_2CO_3$ solution. The precipitate was filtered, strongly washed with cold water, and recrystallized from ethanol to give (PA-1 to PA-8)

**Ultrasonic irradiation method**

VHR was prepared as per the above conventional method in a 50 mL beaker, A solution of (AP1- AP8) (10 mmol) in MeCN (3 mL) was added dropwise to the reaction mixture at 0°C. Reaction flask temp. was brought to r.t. Then the reaction flask was irradiated using the ultrasonic probe at the frequencies of 20 kHz at the required temperature for reaction time [Table 3]. The progress of the reaction was monitored by TLC. Further workup was done as per the above procedure.

**1,3-diphenyl-1H-pyrazole-4-carbaldehyde (PA1)**:

Yield 83.17 %; Yellow Solid; M.P. 144–147°C; $^{1}$H NMR (400 MHz, $CDCl_3$, TMS, ppm): δ= 10.06 (s; 1H), 8.33 (s; 1H), 7.96 (dd; *J*=8.27, 2H), 7.83 (dd; *J*=8.79 Hz; 1H), 7.69 (dd; *J*=7.77 Hz; 2H), 7.55 (d, *J*=8.7 Hz; 2H), 7.55 (dd; *J*=8.19 Hz; 2H), 6.96 (t, *J*=2.4 Hz; 1H); FTIR-ATR: 1670 (C=O), 2786, 2864 (C-H); MS (m/z): $[M^+H]^+$ Calculated for $C_{16}H_{12}N_2O$ 248.28, obtained 249.25. Anal. Calc. for $C_{16}H_{12}N_2O$: C, 77.40; H, 4.87; N, 11.28; O, 6.44. Found: C, 77.33; H, 4.82; N, 11.19%.[27,,28,29]

**3-(4-hydroxyphenyl)-1-phenyl-1H-pyrazole-4-carbaldehyde (PA2)**

Yield 85 %; Light yellow solid; M.P. 210-215°C; $^{1}$H NMR (400 MHz, $CDCl_3$, TMS, ppm): δ= 9.53 (s; 1H), 8.3 (s; 1H), 7.69 (dd; *J*=8.27, 2H), 7.55 (dd; *J*=7.77 Hz; 2H), 7.39 (d, *J*=8.7 Hz; 2H), 7.12 (dd; *J*=8.19 Hz; 2H), 6.80 (d, *J*=8.7 Hz; 1H), 5.23 (s; 1H); $^{13}$C NMR (100 MHz, $CDCl_3$, ppm) δ=191.5 (C=O), 157.5, 152.3, 140.0, 130.3, 129.8, 128.6, 128.4, 128.0, 125.7, 121.2, 121.0, 138.2, 137.1, 107.5; FTIR-ATR: 3558 (O-H), 1730 (C=O), 2788, 2878 (C-H); MS (m/z): $[M^+H]^+$ Calculated for $C_{16}H_{12}N_2O_2$ 264.28, obtained 265.31. Anal. Calc. for $C_{16}H_{12}N_2O_2$: C, 72.72; H, 4.58; N, 10.60; O, 12.11. Found: C, 72.68; H, 4.54; N, 10.40%.[30]

**3-(4-fluorophenyl)-1-phenyl-1H-pyrazole-4-carbaldehyde (PA3)**

Yield 68 %; Light yellow solid; M.P. 173-175°C; $^{1}$H NMR (300 MHz, DMSO-$d_6$, TMS, ppm): δ= 10.11 (s; 1H), 8.4 (s; 1H), 7.82 (dd; *J*=8.37, 2H), 7.77 (dd; *J*=8.1 Hz; 2H), 7.64 (d, *J*=6.4 Hz; 2H), 7.62 (dd; *J*=8.6 Hz; 2H), 7.28 (d, *J*=8.6 Hz; 1H); $^{13}$C NMR (400 MHz, DMSO-$d_6$, ppm) δ=183.7 (C=O), 162.4 (C-F)152.93, 139.72, 133.08, 132.95, 131.84, 129.99, 129.38, 126.11, 122.44, 120.45, 113.6; $^{19}$F NMR (282 MHz, DMSO-$d_6$, ppm): δ=118.32 (s, 1F, 4-F); FTIR-ATR: 1711 (C=O), 1613 (C=N), 1581, 1510 (C=C), 1145 (C-F), 2780, 2836 (C-H); MS (m/z): $[M^+H]^+$ Calculated for $C_{16}H_{11}FN_2O$ 266.27, obtained 267.35. Anal. Calc. for $C_{16}H_{11}FN_2O$: C, 72.17; H, 4.16; F, 7.14; N, 10.52; O, 6.01. Found: C, 72.12; H, 7.16; N, 10.58. %.[31,32]

**3-(4-Methoxyphenyl)-1-phenyl-1H-pyrazole-4-carbaldehyde (PA4)**

Yield 71.93 %; Light yellow solid; M.P. 134-137°C; $^{1}$H NMR (400 MHz, $CDCl_3$, TMS, ppm): δ= 10.06 (s; 1H), 8.54 (s; 1H), 7.8 (dd; *J*=8.37, 2H), 7.68 (dd; *J*=8.0 Hz; 2H), 7.33 (d, *J*=6.0 Hz; 2H), 7.62 (dd; *J*=8.1 Hz; 2H), 7.50 (d, *J*=8.6 Hz; 1H), 3.82 (s; 3H); $^{13}$C NMR (75 MHz, $CDCl_3$, ppm) δ=184.48 (C=O), 160.78, 152.92, 139.82, 130.82, 129.42, 128.39, 126.78, 120.45, 114.65, 108.34, 55.89; FTIR-ATR: 1666 (C=O), 1605 (C=N), 1450,1620 (C=C), 3124 (C-H),

2780, 2836 (C-H), 1026 (C-$OCH_3$); MS (m/z): $[M^+H]^+$ Calculated for $C_{17}H_{14}N_2O_2$ 278.31, obtained 279.26. Anal. Calc. for $C_{17}H_{14}N_2O_2$: C, 73.37; H, 5.07; N, 10.07; O, 11.50. Found: C, 73.31; H, 4.99; N, 10.11%.[33,34,35]

**3-(4-Nitrophenyl)-1-phenyl-1H-pyrazole-4-carbaldehyde (PA5)**

Yield 75.63 %; brown solid; M.P. 165-167°C; $^1$H NMR (300 MHz, $CDCl_3$, TMS, ppm): δ= 10.09 (s; 1H), 8.67 (s; 1H), 8.17 (dd; *J*=7.2, 2H), 8.01 (dd; *J*=9.1 Hz; 2H), 7.8 (d, *J*=5.34 Hz; 2H), 7.6 (dd; *J*=7.6 Hz; 2H), 7.44 (d, *J*=6.6 Hz; 1H); $^{13}$C NMR (75 MHz, $CDCl_3$, ppm) δ=184.45 (C=O), 152.92, 148.65, 139.82, 130.82, 129.89, 128.78, 126.28, 121.38, 120.34, 110.23; FTIR-ATR: 1682 (C=O), 1597 (C=N), 1450, 155 (C=C), 1342, 1520 ($NO_2$), 2783, 2831 (C-H); MS (m/z): $[M^+H]^+$ Calculated for $C_{16}H_{11}N_3O_3$ 293.28, obtained 294.18. Anal. Calc. for $C_{16}H_{11}N_3O_3$: C, 65.53; H, 3.78; N, 14.33; O, 16.37. Found: C, 65.61; H, 3.96; N, 13.99 %.[36,37]

**3-(4-Methylphenyl)-1-phenyl-1H-pyrazole-4-carbaldehyde (PA6)**

Yield 72.43 %; white solid; M.P. 98-100°C; $^1$H NMR (300 MHz, $CDCl_3$, TMS, ppm): δ= 10.04 (s; 1H), 8.45 (s; 1H), 7.85 (dd; *J*=6.2, 2H), 7.36 (dd; *J*=7.18 Hz; 2H), 7.15 (d, *J*=7.45 Hz; 2H), 7.24 (dd; *J*=7.16 Hz; 2H), 6.98 (d, *J*=6.2 Hz; 1H), 2.36 (s; 3H); $^{13}$C NMR (75 MHz, $CDCl_3$, ppm) δ=184.41 (C=O), 152.9, 139.65, 138.82, 130.83, 130.04, 129.1, 129.37, 127.45, 126.80, 108.96, 24.38; FTIR-ATR: 1692 (C=O), 1597 (C=N), 1481, 1627 (C=C), 2924 (C-H); MS (m/z): $[M^+H]^+$ Calculated for $C_{17}H_{14}N_2O$ 262.31, obtained 263.45. Anal. Calc. for $C_{17}H_{14}N_2O$: C, 77.84; H, 5.38; N, 10.68; O, 6.10. Found: C, 77.79; H, 5.42; N, 10.28 %.[38, 39]

**3-(4-Bromophenyl)-1-phenyl-1H-pyrazole-4-carbaldehyde (PA7)**

Yield 67.85 %; Light yellow solid; M.P. 160-162°C; $^1$H NMR (300 MHz, $CDCl_3$, TMS, ppm): δ= 10.06 (s; 1H), 9.03 (s; 1H), 7.82 (dd; *J*=8.37, 2H), 7.77 (dd; *J*=8.1 Hz; 2H), 7.64 (d, *J*=6.4 Hz; 2H), 7.62 (dd; *J*=8.6 Hz; 2H), 7.38 (d, *J*=8.6 Hz; 1H); $^{13}$C NMR (75 MHz, $CDCl_3$, ppm) δ=184.52 (C=O), 152.93, 139.72, 133.08, 132.95, 131.84, 129.99, 129.38, 126.11, 122.44, 120.45, 110.72; FTIR-ATR: 1674 (C=O), 1597 (C=N), 1450, 1566 (C=C), 825 (C-Br), 2780, 2836 (C-H); MS (m/z): $[M^+H]^+$ Calculated for $C_{16}H_{11}BrN_2O$ 327.18, obtained 328.01. Anal. Calc. for $C_{16}H_{11}BrN_2O$: C, 58.74; H, 3.39; Br, 24.42; N, 8.56; O, 4.89. Found: C, 58.59; H, 3.32; Br, 24.45; N, 8.37 %.[40,41]

**3-(4-chorophenyl)-1-phenyl-1H-pyrazole-4-carbaldehyde (PA8)**

Yield 88 %; Yellow solid; M.P. 109-111°C; $^1$H NMR (400 MHz, $CDCl_3$, TMS, ppm): δ= 10.04 (s; 1H), 8.54 (s; 1H), 7.83 (dd; *J*=8.4, 2H), 7.78 (dd; *J*=7.6 Hz; 2H), 7.52 (t, *J*=7.2 Hz; 2H), 7.47 (dd; *J*=8.4 Hz; 2H), 7.41 (t, *J*=7.2 Hz; 1H); FTIR-ATR: 1670 (C=O), 1664 (C=N), 1463, 1571 (C=C), 843 (C-Cl), 2778, 2831 (C-H); MS (m/z): $[M^+H]^+$ Calculated for $C_{16}H_{11}ClN_2O$ 282.72, obtained 283.22, 285.20. Anal. Calc. for $C_{16}H_{11}ClN_2O$: C, 67.97; H, 3.92; Cl, 12.54; N, 9.91; O, 5.66. Found: C, 67.90; H, 3.87; Cl, 12.48; N, 9.96 %.[42,43]

## CONCLUSION:

In summary, we have successfully developed a new protocol for synthesis of 1-phenyl-3-(p-substituted phenyl)-1H-pyrazole-4-carbaldehydes under conventional, sonication and microwave irradiation. We have successfully optimized and used dipolar aprotic green solvent ethanol and acetonitrile, in a synthetic procedure of Pyrazole formylation to avoid reproductive toxicity of traditionally used solvent. Longer reaction times (1-7 hours) under the normal conditions reduced to 10-60 min under sonication, while microwave assisted reactions further reduced the reaction time to only 5-15 minutes. Reactions are conducted with economically cheap and readily available laboratory desktop chemicals with a simple work. Rate enhancements coupled with enhanced reaction yields under sonication and microwave irradiation substantiate that the present work is a good contribution in the area of Vilsmeier-Haack formylation reactions of hydrazone.

## CONFLICT OF INTEREST:

The authors declare no conflict of interest.

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