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MICROWAVE ASSISTED SYNTHESIS OF PYRANO[2,3-C]PYRAZOLE DERIVATIVES UNDER SOLVENT FREE CONDITIONS

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ABSTRACT: A sustainable route for one-pot synthesis of pyrano[2,3-c]pyrazole derivatives using microwave have been used. This approach manifests several green chemistry features like use of operational simplicity, a short reaction time, and remarkable yields of the desired product. The current approach could be a beneficial green alternative for the synthesis of targeted molecules as an alternative to conventional methods

KEYWORDS: Green synthesis, microwave, pyrano[2,3-c]pyrazole.

INTRODUCTION:

Green chemistry is an effective tool in the quest of developing sustainable synthetic techniques[i]. Microwave assisted synthesis is one of the technique. It can be included within the concept of green chemistry since it offers shorter reaction times, improved energy efficiency and offer higher yields[ii]. Synthesis using microwave with proper control of temperature and power is more efficient than conventional heating[iii]. By accelerating reactions, microwave assisted reactions have demonstrated as a reliable and effective method in synthetic organic chemistry.

Heterocyclic compounds are pharmacologically active compounds. According to data, heterocycle is present in more than 85% of all biologically active chemical entities[iv]. Multicomponent reactions provide complex molecules by incorporating diverse moieties in single framework offering molecular diversity[v]. They have various benefits over conventional step synthesis in terms of the ease of purification, relatively mild reactions, short reaction times, atom-efficient synthesis of organic molecules, thereby saving energy and raw material consumption. As a result, multicomponent reactions aids both the economy and the environment, and is used to synthesize desired moiety with enhanced pharmacologically activity.

2-amino-4H-chromenes are a significant class of heterocyclic compounds and have intrigued chemists owing to its diverse biological properties[vi] like antibacterial[vii], antimicrobial[viii], anti-inflammatory[ix], anti-tubercular[x], anticancer[xi]. Pyrazolones are among the oldest synthetic drugs and have garnered prominence since 1883[xii]. It is a five membered lactum ring consisting of

one ketonic group and two nitrogens in its structure. It has wide range of biological activity like anti-microbial[xiii], anti-depressant[xiv], anti-oxidant[xv], anti-tumor[xvi], anti-tuberculosis[xvii], anti-Alzheimer[xviii], anti-inflammatory[xix], anti-viral[xx], etc.

Pyrano[2,3-c]pyrazole[xxi-xxiii] are reported using various catalysts[xxiv-xxviii], ultrasound irradiations [xxix], or under microwave irradiations[xxx]. However, available method have certain drawbacks like prolonged reaction times, the use of toxic solvents, and lower yields. Solvent-free approaches are among the most promising methods for green chemistry.

In order to develop sustainable technique for the synthesis of biologically active heterocyclic scaffolds, we present here the synthesis of pyrano[2,3-c]pyrazole derivatives using microwave under solvent free condition.

EXPERIMENTAL:

Materials and analytical methods

All the chemicals were procured from Sigma Aldrich (India) and were used without additional purification. Merck silica gel 60 F254 plates were used for thin layer chromatography (TLC) to monitor the reaction. Melting points were obtained using open capillary tubes and were uncorrected. Perkin Elmer, Frontier equipment with ATR was used to record FTIR . ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) was recorded on Bruker AVANCE II using TMS as internal standard in DMSO-d6. AB SCIEX 3200 QTRAP mass spectrometer was used to obtain ESI mass spectra and elemental analysis was obtained on model EA300, Euro Vector, Italy.

Procedure for the synthesis of 6-amino-3-methyl-aryl-1,4-dihydropyrano[2,3-c] pyrazole-5- carbonitrile (4a-j)

In a conical flask, the mixture of pyrazolone (1mmol), substituted aldehyde (1mmol) and malononitrile (1mmol), was irradiated using domestic microwave at 400 W for 5 mins. The progress of reaction was monitored using Thin Layer Chromatography (TLC). On completion of reaction, ice-cold water was added to dilute the solid mass. The crude reaction mass was extracted with ethyl acetate, solvent was removed under pressure and the product was purified by recrystallization using ethanol.

6-amino-3-methyl-4-phenyl-1,4-dihydropyrano[2,3-c] pyrazole-5- carbonitrile (4a)

Yield 95% (White solid); **MP=** 244 ^{o}C[xxxi].**IR (υ_{max}/cm^{-1}):** 3369 (NH_2); 3164 (NH); 2191 (CN). **^{1}H NMR (300 MHz, DMSO) δ=** 12.10 (s, 1H, N<u>H</u>), 7.32 (t, J = 7.3 Hz, 2H, Ar-<u>H</u>), 7.25 – 7.15 (m, 3H, Ar-<u>H</u>), 6.88 (s, 2H, N<u>H$_2$</u>), 4.59 (s, 1H, C<u>H</u>), 1.78 (s, 3H, C<u>H$_3$</u>). **^{13}C NMR (75 MHz, DMSO) δ=** 160.83, 154.73, 144.41, 135.53, 128.40, 127.43, 126.69, 120.75, 97.60, 57.15, 36.20 (<u>C</u>H), 9.70 (<u>C</u>H$_3$). **Elemental analysis for $C_{14}H_{12}N_4O$:** C, 66.65; H, 4.79; N, 22.21; found: C, 66.52; H, 4.65; N, 22.08.

6-amino-3-methyl-4-(p-tolyl)-1,4-dihydropyrano[2,3-c] pyrazole-5- carbonitrile (4b)

Yield 95% (White solid); **MP=** 196 ^{o}C[xxxi]. **IR (υ_{max}/cm^{-1}):** 3406 (NH_2); 3313 (NH); 2191 (CN). **^{1}H NMR (300 MHz, DMSO) δ=** 12.08 (s, 1H, N<u>H</u>), 7.08 (dd, J = 22.3, 8.0 Hz, 4H, Ar- <u>H</u>), 6.84 (s, 2H, N<u>H$_2$</u>), 4.54 (s, 1H, C<u>H</u>), 2.27 (s, 3H, C<u>H$_3$</u>), 1.78 (s, 3H, C<u>H$_3$</u>). **^{13}C NMR (75 MHz, DMSO) δ=** 160.73, 154.72, 141.45, 135.67, 135.50, 128.95, 127.32, 120.77, 97.68, 57.34, 35.81 (<u>C</u>H), 20.59 (<u>C</u>H$_3$), 9.72 (<u>C</u>H$_3$). **Elemental analysis for $C_{15}H_{14}N_4O$:** C, 67.65; H, 5.30; N, 21.04; found: C, 67.52; H, 5.28; N, 21.00.

6-amino-4-(2-methoxyphenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (4c)

Yield 92% (White solid); **MP=** 251 ^{o}C [xxxi]. **IR (υ_{max}/cm^{-1}):** 3469 (NH_2); 3306 (NH); 2198 (CN). **^{1}H NMR (300 MHz, DMSO) δ**=11.95 (s, 1H, N<u>H</u>), 7.21 – 7.14 (m, 1H, Ar-<u>H</u>), 7.00 – 6.85 (m, 3H, Ar-<u>H</u>), 6.67 (s, 2H, N<u>H$_2$</u>), 4.98 (s, 1H, C<u>H</u>), 3.80 (s, 3H, OC<u>H$_3$</u>), 1.80 (s, 3H, C<u>H$_3$</u>). **^{13}C NMR (75 MHz, DMSO) δ**= 161.37, 156.24, 155.02, 134.93, 132.03, 128.53, 127.72, 120.72,

120.67, 111.00, 97.70, 95.51, 56.54, 55.42, 9.46 ($\underline{C}H_3$). **Elemental analysis for $C_{15}H_{14}N_4O_2$:** C, 63.82; H, 5.00; N, 19.85; found: C, 63.75; H, 4.84; N, 19.72.

6-amino-4-(4-methoxyphenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (4d)

Yield 97% (White solid); **MP=** 211 ^oC [xxxi]. **IR (υ_{max}/cm^{-1}):** 3482 (NH_2); 3250 (NH); 2189 (CN). **^{1}H NMR (300 MHz, DMSO) δ=** 12.09 (s, 1H, N$\underline{H}$), 7.07 (d, J = 8.6 Hz, 2H, Ar-$\underline{H}$), 6.85 (dd, J = 10.5, 7.5 Hz, 4H, Ar-H, N$\underline{H}_2$), 4.53 (s, 1H, C$\underline{H}$), 3.72 (s, 3H, OC$\underline{H}_3$), 1.78 (s, 3H, C$\underline{H}_3$). **^{13}C NMR (75 MHz, DMSO) δ=** 160.64, 157.92, 154.70, 136.42, 135.55, 128.45, 120.80, 113.72, 97.84, 57.57, 54.95 (O$\underline{C}H_3$), 35.38 ($\underline{C}$H), 9.69 ($\underline{C}H_3$). **Elemental analysis for $C_{15}H_{14}N_4O_2$:** C, 63.82; H, 5.00; N, 19.85; found: C, 63.70; H, 4.82; N, 19.71.

6-amino-4-(3,4-dimethoxyphenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (4e)

Yield 96% (White solid); **MP=** 193-195 ^oC [xxxii]**. IR (υ_{max}/cm^{-1}):** 3372 (NH_2); 3135 (NH); 2184 (CN). **^{1}H NMR (300 MHz, DMSO) δ=** 12.08 (s, 1H, N$\underline{H}$), 6.89 (d, J = 8.3 Hz, 1H, Ar-$\underline{H}$), 6.83 (s, 2H, N$\underline{H}_2$), 6.75 (d, J = 1.4 Hz, 1H, Ar-$\underline{H}$), 6.68 (d, J = 8.2 Hz, 1H, Ar-$\underline{H}$), 4.55 (s, 1H, C$\underline{H}$), 3.72 (s, 3H, OC$\underline{H}_3$), 3.69 (s, 3H, OC$\underline{H}_3$), 1.82 (s, 3H, C$\underline{H}_3$). **^{13}C NMR (75 MHz, DMSO) δ=** 160.71, 154.69, 148.50, 147.52, 136.86, 135.59, 120.82, 119.44, 111.70, 111.16, 97.67, 57.38, 55.43 (O$\underline{C}H_3$), 55.40 (O$\underline{C}H_3$), 35.79 ($\underline{C}$H), 9.80 ($\underline{C}H_3$). **Elemental analysis for $C_{16}H_{16}N_4O_3$:** C, 61.53; H, 5.16; N, 17.94; found: C, 61.45; H, 5.11; N, 17.86.

6-amino-3-methyl-4-(3,4,5-trimethoxyphenyl)-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (4f)

Yield 97% (White solid); **MP=** 226 ^oC [xxxi]. **IR (υ_{max}/cm^{-1}):** 3477 (NH_2); 3305 (NH); 2187 (CN). **^{1}H NMR (300 MHz, DMSO) δ=** 12.09 (s, 1H, N$\underline{H}$), 6.86 (s, 2H, N$\underline{H}_2$), 6.47 (s, 2H, Ar- $\underline{H}$), 4.58 (s, 1H, C$\underline{H}$), 3.72 (s, 6H, 2 x OC$\underline{H}_3$), 3.64 (s, 3H, OC$\underline{H}_3$), 1.87 (s, 3H, C$\underline{H}_3$). **^{13}C NMR (75 MHz, DMSO) δ=** 160.94, 154.68, 152.76, 140.03, 136.16, 135.70, 120.80, 104.59, 97.29, 59.92, 56.91 (O$\underline{C}H_3$), 55.80 (O$\underline{C}H_3$), 36.44 ($\underline{C}$H), 9.89 ($\underline{C}H_3$). **Elemental analysis for $C_{17}H_{18}N_4O_4$:** C, 59.64; H, 5.30; N, 16.37; found: C, 59.56; H, 5.22; N, 16.28.

6-amino-4-(4-chlorophenyl)-3-methyl-1,4-dihydropyrano[2,3-c] pyrazole-5-carbonitrile (4g)

Yield 98% (White solid); **MP=** 233 ^oC [xxxi]. **IR (υ_{max}/cm^{-1}):** 3406 (NH_2); 3306 (NH); 2186 (CN). **^{1}H NMR (300 MHz, DMSO) δ=** 12.15 (s, 1H, N$\underline{H}$), 7.38 (d, J = 8.4 Hz, 2H, Ar-$\underline{H}$), 7.19 (d, J = 8.4 Hz, 2H, Ar-$\underline{H}$), 6.94 (s, 2H, N$\underline{H}_2$), 4.63 (s, 1H, C$\underline{H}$), 1.79 (s, 3H, C$\underline{H}_3$). **^{13}C NMR (75 MHz, DMSO) δ=** 160.87, 154.67, 143.43, 135.66, 131.20, 129.32, 128.42, 120.61, 97.16, 56.74, 35.52 ($\underline{C}$H), 9.69 ($\underline{C}H_3$). **Elemental analysis for $C_{14}H_{11}ClN_4O$:** C, 58.65; H, 3.87; N, 19.54; found: C, 58.52; H, 3.74; N, 19.47.

6-amino-3-methyl-4-(3-nitrophenyl)-1,4-dihydropyrano[2,3-c] pyrazole- 5-carbonitrile (4h)

Yield 98% (Yellow solid); **MP=** 232 ^oC [xxxi]. **IR (υ_{max}/cm^{-1}):** 3472 (NH_2); 3287 (NH); 2193 (CN). **^{1}H NMR (300 MHz, DMSO) δ=** 12.21 (s, 1H, N$\underline{H}$), 8.12 (dt, J = 6.9, 2.2 Hz, 1H, Ar-$\underline{H}$), 8.02 (s, 1H, Ar-$\underline{H}$), 7.69 – 7.61 (m, 2H, Ar-$\underline{H}$), 7.06 (s, 2H, N$\underline{H}_2$), 4.88 (s, 1H, C$\underline{H}$), 1.81 (s, 3H, C$\underline{H}_3$). **^{13}C NMR (75 MHz, DMSO) δ=** 161.11, 154.66, 147.85, 146.79, 135.86, 134.35, 130.21, 121.95, 121.81, 120.47, 96.63, 56.11, 35.61 ($\underline{C}$H), 9.71 ($\underline{C}H_3$). **Elemental analysis for $C_{14}H_{11}N_5O_3$:** C, 56.56; H, 3.73; N, 23.56; found: C, 56.44; H, 3.68; N, 23.47.

6-amino-4-(3-hydroxyphenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (4i)

Yield 95% (White solid); **MP=** 240-241 ^oC. **IR (υ_{max}/cm^{-1}):** 3489 (NH_2); 3350 (NH); 2199 (CN). **^{1}H NMR (300 MHz, DMSO) δ=** 12.10 (s, 1H, N$\underline{H}$), 9.35 (s, 1H, O$\underline{H}$), 7.10 (t, *J* = 7.8 Hz, 1H, Ar-$\underline{H}$), 6.85 (s, 2H, N$\underline{H}_2$), 6.62 (dd, *J* = 6.9, 4.0 Hz, 2H, Ar-$\underline{H}$), 6.55 (s, 1H, Ar-$\underline{H}$), 4.49 (s, 1H, -C$\underline{H}$), 1.82 (s, 3H, C$\underline{H}_3$). **^{13}C NMR (75 MHz, DMSO) δ=** 160.81, 157.37, 154.74,

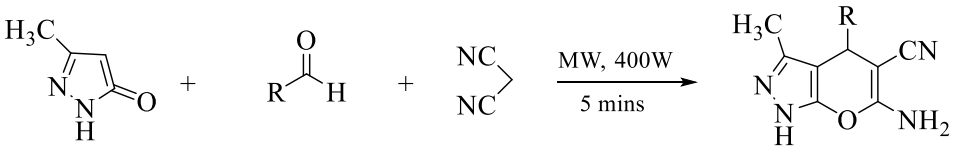
145.90, 135.62, 129.26, 120.79, 118.19, 114.11, 113.84, 97.67, 57.33, 36.14 (CH), 9.71 (CH_3). **Elemental analysis $C_{14}H_{12}N_4O_2$:** C, 62.68; H, 4.51; N, 20.88; found: C, 62.52; H, 4.36; N, 20.82.

6-amino-4-(4-hydroxyphenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (4j)

Yield 965% (White solid); **MP=** 224 ^oC[xxxi]. **IR (υ_{max}/cm^{-1}):** 3468 (NH_2); 3372 (NH); 2199 (CN). **^{1}H NMR (300 MHz, DMSO) δ=** 12.06 (s, 1H, NH), 9.30 (s, 1H, OH), 6.96 (d, *J* = 8.4 Hz, 2H, Ar-H), 6.79 (s, 2H, NH_2), 6.69 (d, *J* = 8.4 Hz, 2H, Ar-H), 4.47 (s, 1H, CH), 1.79 (s, 3H, CH_3). **^{13}C NMR (75 MHz, DMSO) δ=** 160.59, 155.97, 154.71, 135.51, 134.72, 128.40, 120.87, 115.08, 98.03, 57.79, 35.44 (CH), 9.71 (CH_3). **Elemental analysis $C_{14}H_{12}N_4O_2$:** C, 62.68; H, 4.51; N, 20.88; found: C, 62.59; H, 4.32; N, 20.81.

RESULT AND DISCUSSION:

The general path for the synthesis of 6-amino-3-methyl-aryl-1,4-dihydropyrano[2,3-c] pyrazole-5- carbonitrile **4(a-j)** is depicted in Scheme 1. The compounds were synthesized by condensation of pyrazolone (1), substituted aldehyde (2) and malononitrile (3) using domestic microwave at 400 W for 5 mins.



Pyrazolone **1** + Substituted aldehyde **2(a-j)** + Malononitrile **3** → Pyrano[2,3-c]pyrazole derivative **4(a-j)**

R=

a=Phenyl	f=3,4,5-trimethoxyphenyl
b=4-methylphenyl	g=4-chlorophenyl
c=2-methoxyphenyl	h=3-nitrophenyl
d=4-methoxyphenyl	i=3-hydrocyphenyl
e=3,4-dimethoxyphenyl	j=4-hydroxyhenyl

Scheme 1. Synthesis of pyrano[2,3-c]pyrazole derivatives.

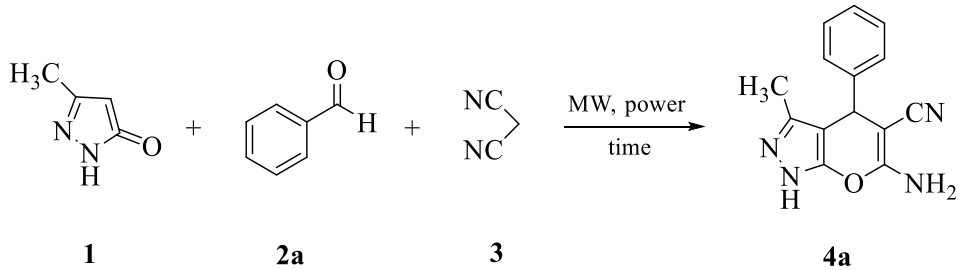
The synthesized compounds were characterized using IR, ^{1}H NMR and the characterization data of synthesized compounds **4(a–j)** are presented in experimental part. In IR spectrum, stretching for NH_2 was observed around 3334-3489 cm^{-1}, a band for NH-stretching was detected in the range of 3135-3372 cm^{-1} and stretching for CN group was observed around 2184-2199 cm^{-1}. In ^{1}H NMR spectrum, a peak around δ = 11.95–12.21 ppm corresponds to NH proton while a peak around δ = 6.67-7.06 ppm denotes NH_2 protons. A peak around δ = 4.47-4.88 ppm corresponds to methine proton (CH) and peak around 1.78-1.87 denotes CH_3. In ^{13}C NMR, peak around 35.38-36.44 denotes methine carbon (CH) and peak around 9.46-9.89 corresponds to CH_3 carbon. The spectral results were in agreement with those reported in the literature. The experimental composition obtained from C, H, N elemental analysis for the synthesized compounds was in good agreement with the theoretical composition. Hereby, confirming that the desired compounds were synthesized.

Optimization of reaction condition:

Initially, we selected pyrazolone (1), benzaldehyde (2a) and malononitrile (3) as model reaction for optimization of time of irradiation and power of microwave. The results are summarized in Table 1. The investigation revealed that reaction efficiency was highly dependent on

microwave power (Table 1, entries 1-3), highest yield was obtained at 400 W. Further we compared the irradiation time of 5, 6, 7 min at 400 W, corresponding yields were 92%, 94%, 95% (Table 1, entries 2, 4 and 5). Hence, further increasing time for 6 mins and 7 mins didn't give significant increase in the yield (Table 1, entries 4 and 5). Hence, 5 mins was considered optimal time for the reaction to complete and 400 W was considered optimal power.

Table 1. Optimization condition for synthesis of pyrano[2,3-c]pyrazole derivatives.



1 **2a** **3** **4a**

Entry	Power (W)	Time (min)	Yield (%)[a]
1	200	5	70
2	400	5	92
3	420	5	88
4	400	6	94
5	400	7	95

Reaction conditions: pyrazolone (1 mmol), benzaldehyde (1 mmol), malononitrile (1 mmol)
[a]Isolated yields

CONCLUSION:

In conclusion, the utilization of microwave-assisted synthesis of the pyrano[2,3-c]pyrazole derivatives has proven to be a highly efficient and innovative method. It offered several advantages, such as ease of operation, short reaction times, and good yields. It's a promising choice owing to its eco-friendly nature.

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