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Research Article

Microwave Assisted Synthesis and Anti-inflammatory Activity of Substituted Pyrazole Derivatives

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A B S T R A C T

Microwave assisted Organic Reaction Enhancement (MORE) has emerged as a new 'lead' in organic synthesis. The technique offers simple, clean, fast, efficient, and economic and environment friendly method for the synthesis of a large number of organic molecules. During our studies, the conventional synthesis of a series of some new substituted 3, 5 dimethyl pyrazole *(4a-c)*, 3-methyl pyrazol-5-one derivatives *(5a-c)*, 3-Methyl- 1- (substituted phenyl) pyrazol-5-ones *(7a-b)* and 2, 3-dimethyl- 1- (substituted phenyl) pyrazol-5-one *(8a-b)* required time (12-16 h) and the yield were often poor (36.9-48.6%). The synthesis of the title compounds using microwave irradiation with an objective to reduce reaction time and increases the yield, all the reaction could be completed in very short duration (4-7 min) with considerable increase in the yields (54-81%) by Using microwave irradiation,. The newly synthesized compounds were evaluated for anti-inflammatory activity.

Keywords: Pyrazole, Pyrazolones, Anti-Inflammatory Activity, More, Microwave Chemistry

Introduction

In the recent years, microwave irradiation reactions have emerged as a new technique in synthesis of organic compound. Important advantages of this technique include highly accelerated rate of the reaction, reduction in reaction time with an improvement in the yield and quality of product. Moreover, the technique is considered as an important approach towards 'green chemistry' because of its eco-friendly nature. synthesis of organic compounds by Conventional methods usually need longer heating time and duration and tedious apparatus set up, results in higher cost of process and the excessive use of chemicals solvents/ reagents leads to environmental pollution.[1]

There are wide varieties of heterocyclic compounds that have been explored for developing pharmacologically important molecules. The pyrazole nucleus has found considerable attention due to outstanding biological activities as antipyretic, analgesic[2] anti-inflammatory[3] antianxiety[4] as well as its good antibacterial and antifungal properties.[5] Encouraged by these literature observations, we have synthesized some novel pyrazole substituted derivatives and evaluate their anti-inflammatory activity.

Substituted 1-Benzoyl-3, 5-dimethyl pyrazole *(4)* was synthesized by treatment of substituted phenyl carbamide *(3)* and acetyl acetone and substituted 1-Benzoyl-3-methyl pyrazol-5-one *(5)* was synthesized by the condensation of substituted phenyl carbamide*(3)* and ethyl acetoacetate. *(Scheme-1)*

2, 3-dimethyl-1- (substituted phenyl) pyrazol-5-one *(8)* was synthesized by the reaction of 3-methyl-(1-substituted phe-

nyl) - pyrazol-5-one *(7)* with dimethyl sulphate *(Scheme-2)*

The new microwave procedures were developed by considering two important parameters: minimum reaction time and maximum yield of the pure product. This was achieved by carrying out each reaction in two major ways. Firstly, optimization of the microwave power (intensity) was performed by conducting the reactions at different microwave powers/ intensities (250, 350 & 700W) setting for a fixed time of five minutes. The microwave intensity giving the maximum yield was selected for optimizing the reaction time. Each time, the product was isolated; the yield and quality of the product was compared with the one obtained by conventional method. Finally, by using the optimized microwave intensity and time, each reaction was repeated at least three times and the products were compared with the conventional products by studying their melting point, mixed melting point, TLC, Co-TLC and IR spectra. The comparative results for optimized procedures are given in Table-1.

Materials and Methods

All the chemicals used were obtained from S.D. Fine Chem. Ltd., Mumbai and E-Merck Ltd., Mumbai while the reagents and solvents were of analytical grade. Heating was done in a microwave oven (LG-Healthcare System, MG-605 AP and 900 W). The melting points were carried out in open capillary tube and were uncorrected. Thin layer chromatography was performed using silica gel coated on a glass plate. IR spectra in KBr disc and the absorption bands are expressed in cm^{-1} were recorded on a Shimadzu 8201 PC FTIR ($u_{max\ in}$ cm^{-1}) spectrophotometer. ^1H NMR spectra were recorded in $CDCl_3$+acetone-d_6 on a FX 90Q FTNMR spectrometer using TMS as an internal standard (chemical shifts in δ, ppm). The reactions were monitored by thin layer chromatography on silica gel G coated glass plates using benzene: ethyl acetate (7:3) solvent system. The purity of synthesized compounds was ascertained by TLC using iodine vapors as detecting agents.

General Procedure

Synthesis of Substituted 1-Benzoyl-3, 5-dimethyl pyrazole (4a-c):

Conventional methods:

A mixture of 1.3g of substituted phenyl carbamide (10.0 mmol) and 1g of acetyl acetone (10.0 mmol) was refluxed in 25 ml of methanol and 1 ml of concentrated hydrochloric acid for 12 hours on a water bath. The resulting solution was then concentrated and cooled at room temperature. The solid thus separated was washed with methanol and recrystallized with ethanol.

Microwave method:

To a mixture of substituted phenyl carbamide (1.3g, 10.0 mmol) and acetyl acetone (1g, 10.0 mmol) in methanol (5ml), a few drops of concentrated hydrochloric acid (1 ml) were added and the reaction mixture was placed in a conical flask, covered with a glass funnel. The reaction mixture was irradiated in 30 second increment at different microwave intensities for different duration by following the pulse heating approach. A 'heat sink' beaker containing water) was also kept in the oven. A TLC was run after every one minute of microwave irradiation using benzene: ethyl acetate (7:3) solvent system for the monitoring the progress of reaction. After completion of reaction, the procedure was done in a similar manner of conventional procedure.

1-Benzoyl-3, 5-dimethyl pyrazole (4a)

Yield-54.9 %, m.p. 176-178°C, *IR (KBr) ν cm^{-1}* : 3116.75 (aromatic C-H stretching), 2941.24 (asymmetric (CH_3) (C-H stretching), 2883.38 (symmetric (CH_3) (C-H) stretching, 1670.24 (C=O stretching), 1598.86 (C=N stretching), 1446.51 (C=C stretching) and 842.83 (C-N stretching). *^1H-NMR ($CDCl_3$): δ ppm* 2.42 (s, 6H, CH_3), 6.15 (s, 1H CH-pyrazole), 7.44-7.48 (m, 2H, $H_{3,5}$ 1-benzoyl), 7.57 (m, 1H, H_4 1-benzoyl), 8.02-8.04 (d, 2H, $H_{2,6}$ 1-benzoyl). *^{13}CNMR ($CDCl_3$): δ ppm*, 190(C=O), 147(2C, C-3&C-5, Pyrazole), 136.7(C-1, phenyl), 134.3(C-4, phenyl), 129.7(2C, C-2&C-6, phenyl), 129.0(2C, C-3&C-5, phenyl), 106(C-1, phenyl), 13.8(CH_3), 7.1(CH_3)

Calcd for $C_{12}H_{12}N_2O$: C, 72.0; H, 6.0; N, 14.0. Found: C, 69.97; H, 5.98; N, 13.97.

1-(2-Hydroxy benzoyl)-3, 5-dimethyl pyrazole (4b)

m.p. 188-190°C. *IR (KBr) ν cm^{-1}* : 3595 (O-H stretching), 3392 (aromaticC-H stretching), 2941.24 (asymmetric (CH_3) (C-H stretching), 2885.31(symmetric (CH_3)(C-H) stretching, 1718.46 (CO-N-CO), 1683.74 (C=O stretching), 1598.88 (C=N stretching), 1446.51, 1469.66, 1494.73, 1521.73 (C=C ring stretching) and 1232, 1188.07 (C-O stretching) *^1H-NMR ($CDCl_3$): δ ppm* 2.49 (s, 6H, CH_3), 6.08 (s, 1H CH- pyrazole), 6.87-6.96 (m, 2H, $H_{4,5}$ 2-hydroxy benzoyl), 7.41-7.43 (d, 1H, H_6 2-hydroxy benzoyl), 10.93 (s, 1H, OH). *^{13}CNMR ($CDCl_3$): δ ppm*, 190(C=O),158.5(C-2 phenyl), 147(2C, C-3&C-5, Pyrazole), 135.7(C-4, phenyl), 131.1(C-6, phenyl),123.9(C-1, phenyl), 121.6 (C-5, phenyl), 116.2(C-3,phenyl), 106(C-1, phenyl), 13.8(CH_3), 7.1(CH_3).

Calcd for $C_{11}H_{10}N_2O_3$: C, 66.67; H, 5.56; N, 12.96. Found: C, 66.64; H, 5.54; N, 12.97.

1-(4-Hydroxy benzoyl)-3, 5-dimethyl pyrazole (4c)

m.p. 182-184°C, *IR (KBr) ν cm^{-1}* : 3609 (O-H stretching), 3304.43,3040 (aromatic C-H stretching), 2960 (asymmetric (CH_3) (C-H stretching), 1679.64 (C=O stretching), 1587 (C=N stretching), 1431 (C=C stretching) and 1190 (C-O stretching) *^1H-NMR ($CDCl_3$): δ ppm* 2.17 (s, 3H, CH_3), 2.49 (s, 3H, CH_3), 6.06 (s, 1H CH- pyrazole), 6.84-6.88(d, 2H, $H_{2,6}$ 1-benzoyl), 7.86-7.89 (d, 2H, $H_{3,5}$ 1-benzoyl), 9.63 (s,

1H, CHO).[13] CNMR ($CDCl_3$): δ ppm, 190(C=O),163.1(C-4, phenyl), 147(2C, C-3&C-5, Pyrazole), 131.1(2C, C-2&C-6, phenyl), 129.3(C-1, phenyl), 116.2(2C, C-3&C-5, phenyl), 106(C-1, phenyl), 13.8(CH_3), 7.1(CH_3).

Calcd for $C_{12}H_{12}N_2O_2$: C, 66.67; H, 5.56; N, 13.0. Found: C, 66.64; H, 5.54; N, 12.97.

Synthesis of Substituted 1-Benzoyl-3-methyl pyrazol-5-one (5a-c):

Conventional methods:

A mixture of 1.3 g substituted phenyl carbamide (10.0 mmol) and 0.13 g of ethyl acetoacetate (10.0 mmol) was refluxed in 25 ml methanol, containing 1.0 ml of concentrated hydrochloric acid for 10 hours on a water bath. The resulting solution was cooled and concentrated at room temperature. The solid, filtered washed with methanol, dried and recrystallized with acetone.

Microwave method:

To a mixture of substituted phenyl carbamide (1.3g, 10.0 mmol) and ethyl acetoacetate (0.13 g, 10.0 mmol) in methanol (5ml), a few drops of concentrated hydrochloric acid (1 ml) were added and the reaction mixture was placed in a conical flask, covered with a glass funnel. The reaction mixture was irradiated in 30 second increment at different microwave intensities for different duration by following the pulse heating approach. A 'heat sink' beaker containing water) was also kept in the oven. A TLC was run after every one minute of microwave irradiation using benzene: ethyl acetate (7:3) solvent system for the monitoring the progress of reaction. After completion of reaction, the procedure was done in a similar manner of conventional procedure.

1-Benzoyl-3-methyl pyrazol-5-one (5a)

m.p. 128-130°C, *IR (KBr) ν cm*$^{-1}$: 3033 (aromatic C-H stretching), 2941 (asymmetric (CH_3) (C-H stretching), 2883 (symmetric (CH_3) (C-H) stretching, 1670 (C=O stretching), 1598 (C=N stretching), 1431 (C=C stretching) and 842 (C-N stretching)

^{1}H-NMR (DMSO): δ ppm 2.57 (s, 3H, CH_3), 5.26 (s, 2H CH_2-pyrazole), 6.84-6.87 (m, 3H, $H_{3,4,5}$ 1-benzoyl), 7.85-7.88 (d, 2H, $H_{2,6}$ 1-benzoyl). *^{13}CNMR ($CDCl_3$): δ ppm*, 171(C=O, pyrazolones), 167.7(C=O), 155.6(C-3, pyrazolone), 133.5 (C-1, phenyl), 131.9(C-4, phenyl), 128.6(2C, C-3&C-5, phenyl) 127.3(2C, C-2&C-6, phenyl) 35.3(C-4, pyrazolone), 19.7(CH_3)

Calcd for $C_{11}H_{10}N_2O_2$: C, 65.34; H, 4.95; N, 13.86. Found: C, 65.30; H, 4.92; N, 13.84.

1-(2-Hydroxy benzoyl)-3-methyl pyrazol-5-one (5b)

m.p. 128-130°C, *IR (KBr) ν cm*$^{-1}$: 3608, (O-H stretching), 3024 (aromatic C-H stretching), 2933 (asymmetric (CH_3) (C-H stretching), 1608(C=O stretching), 1550, 1488 (C=N stretching), 1436, 1448, 1458 (C=C ring stretching) and 1240 (C-O stretching)

^{1}H-NMR (DMSO): δ ppm 2.49 (s, 3H, CH_3), 5.47 (s, 2H CH_2-pyrazole), 6.87-6.96 (m, 2H, $H_{4,5}$ 2-hydroxybenzoyl), 7.41-7.43 (d, 1H, H_6 2-hydroxy benzoyl), 7.98-8.00 (d, 1H, H_3 2-hydroxy benzoyl), 10.34 (s,1H,OH).[13] *CNMR ($CDCl_3$): δ ppm*, 171(C=O, pyrazolones), 167.7(C=O),156.1(C-2, phenyl), 155.6(C-3, pyrazolone),133.3(C-4, phenyl),128.7(C-6,phenyl),121.2(C-5, phenyl),120.7(C-1,phenyl), 115.8(C-3,phenyl) 35.3(C-4, pyrazolone), 19.7(CH_3).

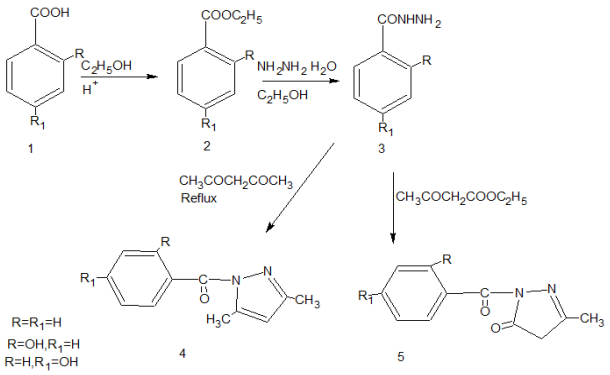
Calcd for $C_{11}H_{10}N_2O_3$: C, 60.56; H, 4.59; N, 12.84. Found: C, 60.52; H, 4.56; N, 12.80.

1-(4-Hydroxy benzoyl)-3-methyl pyrazol-5-one (5c)

m.p. 128-130°C. *IR (KBr) ν cm*$^{-1}$: 3610 (O-H stretching), 3053.11 (aromatic C-H stretching), 3006.82 (C-H stretching of CH_3), 1718.46 (CO-N-CO), 1668.31(C=O stretching), 1631.67 (C=N stretching), 1579.59, 1535.23, 1487.01, 1434.94 (C=C stretching), 1238.21 (C-O stretching) and 869.84 (C-N stretching).

^{1}H-NMR (DMSO): δ ppm 2.57 (s, 3H, CH_3), 5.47 (s, 2H CH_2-pyrazole), 7.43-7.47 (d, 2H, $H_{2,6}$ 1-benzoyl), 7.96-8.01 (d, 2H, $H_{3,5}$ 1-benzoyl), 10.34 (s ,1H, OH). *^{13}CNMR ($CDCl_3$): δ ppm*, 171(C=O, pyrazolones), 167.7(C=O), 160.7(C-4, phenyl), 155.6(C-3, pyrazolone), 128.7(2C, C-2&C-6 phenyl), 126.1(C-1, phenyl), 115.8(2C, C-3&C-5, phenyl), 35.3(C-4, pyrazolone), 19.7(CH_3).

Calcd for $C_{11}H_{10}N_2O_3$: C, 60.56; H, 4.59; N, 12.84. Found: C, 60.59; H, 4.58; N, 12.81.



Scheme I

3-Methyl- 1-(substituted phenyl) pyrazol-5-ones (7a-b)

Conventional methods:

Ethyl acetoacetate (3.10 g, 6.52 mmol) and 1.0 g (6.52 mmol) of substituted phenyl hydrazine were mixed together in an evaporating dish. The mixture was heated on a boiling water bath in a fume cupboard for 2.5 hours and stirred from time to time with a glass rod. The heavy reddish syrup was allowed to cool, 10.0 ml of ether was added and the mixture was stirred vigorously. The syrup was solidified within 15

minutes. The solid, filtered at pump and washed thoroughly with ether to remove colored impurities. Recrystallised from equal volume of ethanol and water.

Microwave method:

To a mixture of ethyl acetoacetate (3.10 g, 6.52 mmol) and 1.0 g (6.52 mmol) of substituted phenyl hydrazine were mixed together in an evaporating dish, covered with a watch glass. The reaction mixture was irradiated in 30 second increment at different microwave intensities for different duration by following the pulse heating approach. A 'heat sink' beaker containing water) was also kept in the oven. A TLC was run after every one minute of microwave irradiation using benzene: ethyl acetate (7:3) solvent system for the monitoring the progress of reaction. After completion of reaction, the procedure was done in a similar manner of conventional procedure.

3-Methyl- 1-(4-nitro phenyl) pyrazol-5-ones (7a)

m.p. 82-84°C. *IR (KBr) v* cm^{-1} : 3516 (N-H stretching), 3316. (aromatic C-H stretching), 2977 (C-H stretching of CH_3), 1713 (C=O stretching), 1596(C=C stretching), 1495 (asymmetric ($ArNO_2$) $(N=O)_2$ stretching), 1394 (symmetric ($ArNO_2$) $(N=O)_2$ stretching) and 838 (C-N stretching)

^{1}H-NMR ($CDCl_3$): δ ppm 3.10 (s, 3H, CH_3), 5.28 (s, 1H, CH), 7.04-7.07 (d, 2H, $H_{2,6}$ 1-nitrophenyl), 8.12-8.14 (d, 2H, $H_{3,5}$ 1-nitrophenyl), 10.29(s, broad, 1H, NH). *^{13}CNMR ($CDCl_3$): δ ppm*, 168(C=O, pyrazolone), 155.6(C-3, pyrazolone), 140(C-4, phenyl), 135.9(C-1, phenyl), 134.8(C-5, phenyl) 125.0(C-2, phenyl), 123.8(C-3, phenyl), 121.3(C-6, phenyl), 20.3(CH_3)

Calcd for $C_{10}H_9N_3O_3$: C, 54.79; H, 4.10; N, 19.17. Found: C, 54.75; H, 4.07; N, 19.14.

3-Methyl- 1-(2, 4-dinitro phenyl) - pyrazol-5-one (7b)

m.p. 66-68°C. IR (KBr) v cm^{-1} : 3309 (N-H stretching), 3100(C-H stretching), 2977 (C-H stretching of CH_3), 1725 (C=O stretching),1698, 1594(C=C stretching), 1512 (asymmetric ($ArNO_2$) $(N=O)_2$ stretching), 1423 (symmetric ($ArNO_2$) $(N=O)_2$ stretching) and 833 (C-N stretching)

^{1}H-NMR ($CDCl_3$): δ ppm 1.29 (s, 3H, CH_3), 5.26 (s, 1H, CH), 8.12-8.14 (d, 2H, $H_{5,6}$ 2,4-dinitrophenyl), 8.52 (s, 1H, H_3, 2,4-dinitrophenyl), 10.29 (s,broad,1H, NH). *^{13}CNMR ($CDCl_3$): δ ppm*, 168(C=O, pyrazolone), 155.6(C-3, pyrazolone), 144(C-4, phenyl), 142(C-1, phenyl), 141.0(C-2, phenyl), 129.9(C-5, phenyl) 122.8(C-6, phenyl), 118.9(C-3, phenyl), 20.3(CH_3).

Calcd for $C_{10}H_8N_4O_5$: C, 45.45; H, 3.03; N, 21.21. Found: C, 45.42; H, 3.06; N, 21.18.

2, 3-Dimethyl- 1-substituted phenyl - pyrazol-5-one (8a-b)

Conventional methods:

In a 50 ml of three necked flask, fitted with a dropping funnel, a double surface condenser with sealed stirrer was set up in a fume cupboard. A solution of 0.5 g of sodium hydroxide in small volume of water was mixed in solution of 1.40 g (5.73 mmol) of 3-methyl-1-substituted phenyl- pyrazol-5-one(7) in 1.0 ml of methanol and 0.72 g (0.54 ml, 5.73 mmol) of dimethyl sulphate was added. The mixture was warmed on a water bath the mixture was refluxed for 1 hour and allowed to cool, with continuous stirring. Methanol was distilled off, hot water was added to the residue, filtered from impurities, 2, 3-dimethyl-1-substituted phenyl-pyrazol-5-one was extracted with benzene and solvent was evaporated. The crude product was recrystallised from benzene.

Microwave methods:

To a mixture of 0.5 g of sodium hydroxide in small volume of water was placed in solution of 1.40 g (5.73 mmol) of 3-methyl-1-substituted phenyl- pyrazol-5-one (7) in 1.0 ml of methanol and 0.72 g (0.54 ml, 5.73 mmol) of dimethyl sulphate was added and the reaction mixture was placed in a conical flask, covered with a glass funnel. The reaction mixture was irradiated in 30 second increment at different microwave intensities for different duration by following the pulse heating approach. A 'heat sink' beaker containing water) was also kept in the oven. A TLC was run after every one minute of microwave irradiation using benzene: ethyl acetate (7:3) solvent system for the monitoring the progress of reaction. After completion of reaction, the procedure was done in a similar manner of conventional procedure

2, 3-Dimethyl- 1-(4-nitro phenyl) - pyrazol-5-one (8a)

m.p. 224-226°C, *IR (KBr) v* cm^{-1} *:* 3467(C-H stretching), 2977(C-H stretching of CH_3), 1636 (C=O stretch)ing),1498 (C=C stretching), 1447 (asymmetric ($ArNO_2$) $(N=O)_2$ stretching), 1322(symmetric ($ArNO_2$) $(N=O)_2$ stretching) and 849 (C-N stretching)

^{1}H-NMR (DMSO): δ ppm 1.27 (s, 3H, CH_3), 2.01 (s, 3H, CH_3), 3.39 (s, 1H, CH), 7.04-7.07(d, 2H, $H_{2,6}$ 1-nitrophenyl), 8.12-8.14 (d, 2H, $H_{3,5}$ 1-nitrophenyl). *^{13}CNMR ($CDCl_3$): δ ppm*, 160.7(C=O, pyrazolone), 159.6(C-3, pyrazolone), 141(C-4, phenyl), 139.0(C-1, phenyl), 135.4(C-5, phenyl), 131.9(C-3, phenyl), 119.2(C-2, phenyl), 124.1(C-6, phenyl),95.4(C-4, pyrazolone), 35.3(CH_3-N, pyrazolone), 24.0(CH_3)

Calcd for $C_{11}H_{11}N_3O_3$: C, 56.65; H, 4.72; N, 18.03. Found: C, 56.63; H, 4.70; N, 18.06.

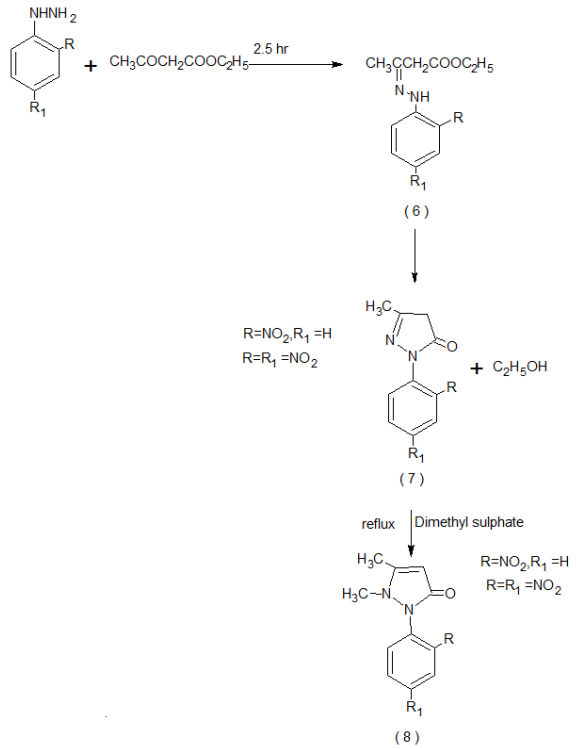
2, 3-Dimethyl- 1-(2, 4-dinitro phenyl) - pyrazol-5-one (8b)

Yield-40 %, m.p. 240-242°C, *IR (KBr) v* cm^{-1}: 3100(C-H stretching), 2977 (C-H stretching of CH_3), 1725 (C=O stretching), 1594(C=C stretching), 1512 (asymmetric ($ArNO_2$) $(N=O)_2$ stretching), 1423 (symmetric ($ArNO_2$) $(N=O)_2$ stretching) and 833 (C-N stretching)

^{1}H-NMR (DMSO): δ ppm 1.31(s, 3H, CH_3), 2.57(s, 3H, CH_3),

5.26(s, 1H, CH), 8.12-8.14(d, 2H, $H_{5,6}$ 2,4-dinitrophenyl), 8.52(s, 1H, H_3 2,4-dinitrophenyl). ^{13}CNMR ($CDCl_3$): δ ppm, 160.7(C=O, pyrazolone), 159.6(C-3, pyrazolone), 142.4(C-4, phenyl), 139.4(C-1, phenyl), 132.2(C-2, phenyl), 130.4(C-5, phenyl),119.2(C-3, phenyl) 113.1(C-6, phenyl),95.4(C-4, pyrazolone), 35.3(CH_3-N, pyrazolone), 24.0(CH_3)

Calcd for $C_{10}H_8N_4O_5$: C, 47.48; H, 3.60;N, 20.14 . Found: C, 47.45; H, 3.62; N, 20.11.



Scheme 2

Table 1.Comparative reaction time and percentage yield of synthesized compounds by conventional & microwave method

Compd no.	Reaction time		Yield (%)	
	Conventional (h)	MW (min)	Conventional	MW
4a	11	5	39.0	70.7
4b	12	4	44.0	76.4
4c	11	6	43.5	80.5
5a	14	6	36.7	74.6
5b	12	4	42.6	67.9
5c	10	6	41.5	65.9
7a	4	2	48.5	67
7b	5	1.5	52	78
8a	3	2	59	89
8b	4	2	63	87

Anti-inflammatory Activity

Evaluation of the anti-inflammatory activity of newly synthesized substituted pyrazole series were carried by the method of Winter et al[10]-carrageenan induced rat paw edema method in Wistar albino rats. The anti-inflammatory activity of the newly synthesized compounds was compared, using indomethacin as standard drug. The synthesized compounds were suspended in 2% Tween 80. Percentage reduction in paw edema at 4 hr in comparison to the control is given in Table-2.

Table 2.Anti-inflammatory activity of synthesized compounds

Comp.	R	R_1	Anti-inflammatory (% inhibition±SEM)
Control			-
Indomethacine			61.50±1.19*
4a	H	H	-
4b	OH	H	49.06±1.08*
4c	H	OH	56.51±1.14*
5a	H	H	-
5b	OH	H	31.25±1.10
5c	H	OH	53.12±1.44*
7a	NO_2	H	74.21±1.32
7b	H	NO_2	76.25±2.98*
8a	NO_2	H	44.37±1.51*
8b	H	NO_2	17.80±1.00

Result and Discussion

A new microwave procedure for the rapid and efficient synthesis of substituted 3, 5 dimethyl pyrazole *(4a-c)*, 3-methyl pyrazol-5-one derivatives *(5a-c),* 3-Methyl-1-(substituted phenyl) pyrazol-5-ones *(7a-b)* and 2, 3-dimethyl-1- (substituted phenyl) pyrazol-5-one *(8a-b)* has been developed. The microwave heating effectively reduced the reaction time from 10-14 h to a few minutes (4-7 min). By using microwave irradiation for heating, all the ten compounds were prepared in yields that were appreciably more than the conventional methods.

Highest yield improvement of about 91% was observed for compound 4c and 8b, when compared with conventional method. The quality of the products formed was found to be better showing less number of impurities on TLC when compared to the conventional products. The physical, chemical and spectral (IR, ^{1}HNMR and ^{13}CNMR) properties of the microwave reaction products were found to be the same when compared with the conventional products prepared simultaneously. The experiment could be conducted in much shorter duration by new microwave methods. From

the result, it was observed that all the test compounds possessed significant anti-inflammatory activity.

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References

1. Sharma SV et al. MORE Chemistry: An Eco-friendly Synthetic Technique. *Indian J Pharm Sci* 2002; 64: 337.
2. Kost AN, Grandberg I. Progress in pyrazole chemistry. *Adv Heterocycl Chem* 1966; 6: 347-429.
3. Sammes MP. The 3H-Pyrazoles Adv. Heterocycle. *Chem*, 1983; 34: 38.
4. Eid Al. (E)-3, 5-Dimethyl-1-p-tolyl-4-(p-tolyldiazenyl)-1H-pyrazole. *J Pharm Belg* 1978; 33: 303.
5. Hermann E. Synthesis, characterization and spectral studies of new 4(Substituted phenyl hydrazono)-NI -(R)- amino malonyl-3-ethyl-2-Pyrazolin-5-one and 3-methyl-4(Substitutedphenyl hydrazono)-Isoxazolone. Cancer Chemother Rept. 1961; 14: 85.
6. Haufel J. Regioselective formylation and chemoselective oxidation of 1, 3, 5-triaryl pyrazoline: Synthesis of 4- (3,5-diaryl-1H-pyrazol-1-yl) benzaldehydes. *Angew Chem* 1974; 13: 604.
7. Habib NS. Ionic Liquid as an Efficient Promoting Medium for Synthesis of Bis-pyrazolo[3,4-b:4,3- e]pyridines. *Sci Pharm* 1981; 49: 42.
8. Habib NS. Ionic Liquid as an Efficient Promoting Medium for Synthesis of Bis-pyrazolo[3,4-b:4,3- e]pyridines. *Sci Pharm* 1981; 49: 42.
9. Winter CA, Risley EA, Nus GN. Carragenean-induced edema in hind paw of the rat as an assay for antiinflammatory drugs. *Proc Soc Exp Biol* 1962; 111: 544-547.