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RESEARCH ARTICLE

Microwave Assisted one Pot Synthesis of Pharmaceutical Pyrazole Derivatives

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ABSTRACT

A simple, efficient and one pot microwave assisted synthesis of (5-amino-3-aryl-1H-pyrazol-1-yl) (6-chloropyrazin-2-yl) methanones is described. The molecules were synthesized by the cyclocondensation reaction of 6-chloropyrazine-2-carboxylic acid hydrazide and substituted benzoylacetonitriles by irradiation under microwave energy, to provide in high yields with clean and scalable reactions. The synthesized compounds were characterized by IR, 1H-NMR and mass spectral data. The plausible mechanism of the reaction is proposed.

Keywords: Microwave, Pyrazole, Cyclocondensation, Characterization.

INTRODUCTION

Pyrazole derivatives constitute an interesting class of N-containing hetero cycles, which are associated with diverse chemical and pharmacological properties (1-4). Pyrazole derivatives exhibits vast spectrum of biological activities like anti inflammatory, antidepressant, antimicrobial, antitumor and antitubercular properties (5). Some substituted pyrazole derivatives are also associated with high end medical applications in the field of cardiovascular drugs, acting as vasodilators, calcium channel blockers, potassfum channel inhibitors and apoptosis inducers. (6)

Pyrazoles are key reagents of multicompenent of heterocyclizations. The heterocycles possessing pyrazole nucleus provides an facile synthetic approach for obtaining heterocyclic systems moreover of studying mechanisms of pyrazoles also exhibit rich synthetic potential for obtaining skeleton frame work of 5,6 and 7 membered heterocycles. Literature survey cites numerous methods of synthesizing pyrazole nucleus by microwave irradiation (7-13). The use of microwave irradiation for carrying out organic reactions shows excellent results, which are eco-friendly and falls in the domain of green chemistry. Microwave assisted organic synthesis offers a rapid, reproducible and scalable process to synthesize new molecules in high yield. Moreover the formation of heterocyclic rings by cyclization reactions is typically a process which is well-suited for microwave methodology. Such cyclization reactions often requires high temperature and longer reaction time for completion of the reaction but microwave heating results in rapid reaction rate, higher yields and cleaner reaction profiles (14-17).

Prompted by these observations and in continuation of our work on microwave assisted synthesis of heterocycles, we herein report the one pot synthesis of 5-amino-3-aryl-pyrazol-1-yl) (6-chloropriazine-2-yl)-methanones (3a-g). The acid catalyzed cyclocondensation reaction was carried out between (6-chloropriazine-2-carboxylic acid hydrazide (1) and substituted benzoylacetonitriles (3). (6-Chloropriazine-2-carboxylic acid hydrazide (1) was synthesized by the method reported in the literature (18).

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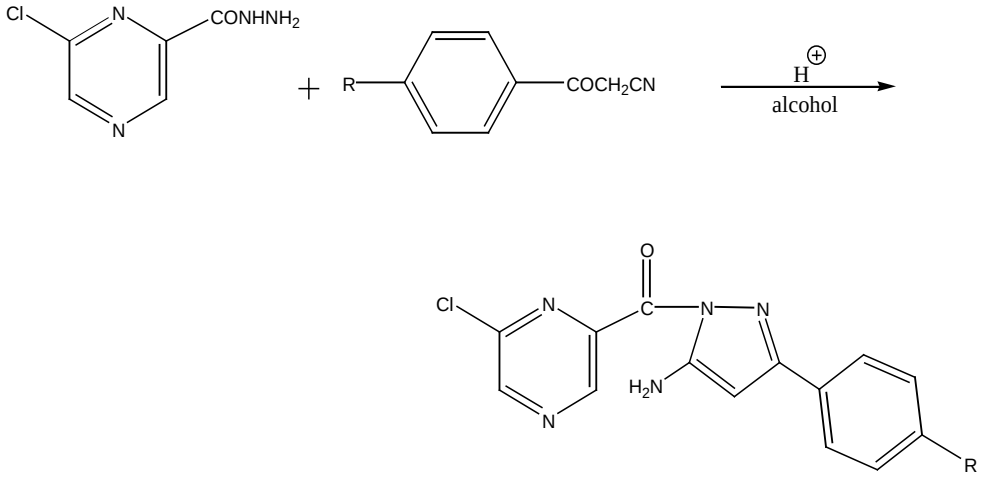
Glacial acetic was employed in the reaction, which act as acyclo condensation catalyst and microwave energy transfer improver. Polar, protic solvent methnol was employed as a solvent.

RESULT AND DISCUSSION

The preparation of (5-amino-3-aryl-pyrazol-1-yl)-(6-chloropyrazin-2-yl)-methanones (3a-g) was synthesized in present investigated (Scheme 1). The reaction was carried out employing microwave irradiation for appropriate time (10 to 15 minutes), afforded high yields (72-82%) with complete conversion of reactants. The constitution of newly synthesized (3a-g) was established by IR, ^{1}H NMR and MS spectroscopy. A plausible mechanism (Scheme 2) was proposed for the above reaction. The mechanism supported and was in accordance with the formation of(5-amino-3-aryl-pyrazol-1-yl)-(6-chloropyrazin-2-yl)-methanones (3a-g).

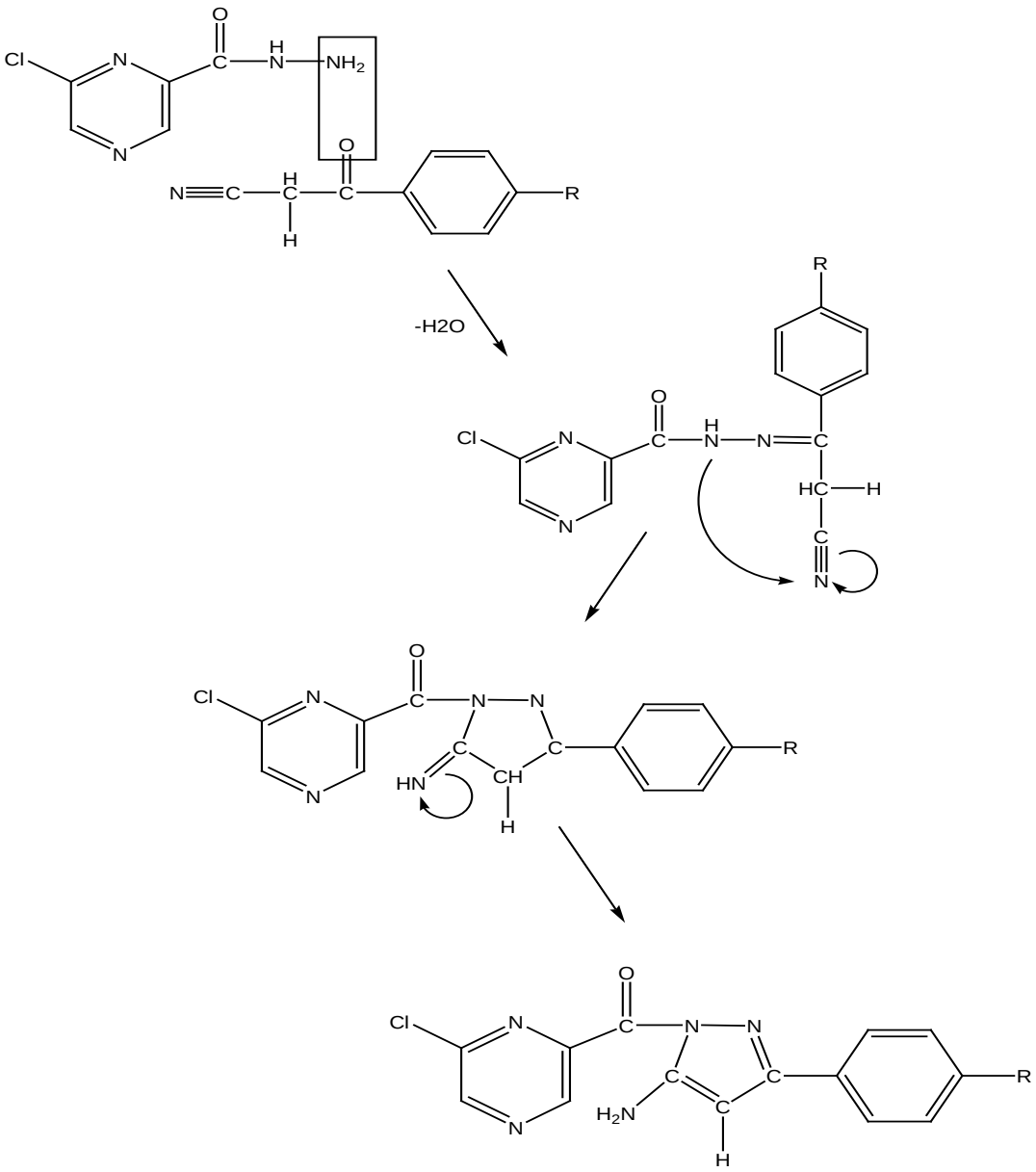
Scheme 1: Synthesis of (5-amino-1-aryl-pyrazol-1-yl) (6-chloropyrazin methanol)**:**

Where, R = -H, -2(Cl), -3(Cl),-4(Cl),-4(Br), -3(CH_3),-4(CH_3),-4(OCH_3).



Scheme 2

Mechanism of the reaction



CONCLUSIONS

The described synthetic protocol allows for the preparation of a series of (5-amino-3-aryl-pyrazol-1-yl)(6-chloropyrazin-2-yl)-methanones as new structures which can be potentially useful in various pharmacological applications. A microwave assisted synthesis was develoved which lead to rate enhancement, higher yields, less side reactions and a better reproducibility compared to conventional heating modes.

EXPERIMENTAL SECTION

The melting points were taken on an electrothermal capillary melting point apparatus and are uncorrected. All solvents were of AR grade and were dried before use. The benzoylaietnitries were procured from Lancaster chemicals and Alfa Aeser chemicals, were used as received. Microwave assisted synthesis was performed on a CEM Microwave synthesizer (Discover Model). The elemental analyses was carried out on a VarioElementa model CHNS

analyzer. The percentages recorded were within ±0.4% of the theoretical values. The IR spectra were recorded in KBr on a Perkin Elmer FTIR spectrophotometer.^{1}H-NMR spectra were recorded on a Bruker 300 Avance Spectrometer (300MHz); chemical shifts (δ scale) were reported in parts per million (ppm) using DMSO-$d_6$as a solvent and TMS as an internal standard. ^{1}H-NMR spectra were reported in order: multiplicity and number of protons; signals were characterized as s (singlets), d(doublet), and m (multiplet). The mass spectra were recorded on a Jeol-JMS-D300 mass spectrometer, operating at 70eV. The progress of all the reactions were monitored by TLC using pre-coated silica gel plates (Merck) and spots were visualized against UV light.

Generalprocedure for the synthesis of (5-amino-3-aryl-pyrazol-1-yl)(6-chloropyrazin-2-yl)-methanones (3a-g):

A mixture of (6-chloropriazine-2-carboxylic acid hydrazide (1) (0.001 mole), benzoyl nitriles (2)(0.001 mole), catalytic amount of glacial acetic acid (≈5-6 drops) and dry methanol (2 mL) was subjected to microwave irradiation for appropriate time (Table 1). The progress of the reaction was monitored on TLC. After the completion of reaction, the reaction mixture was quenched in ice water and resulting crude residue was filtered, dried and recrystallized from chloroform.

Table 1

Compounds	Molecular Formula	Mol. Wt.	MP (0c)	Yield (%)	Time (min)
3a	$C_{14}H_{11}ON_5Cl$	316.5	237	82	12
3b	$C_{14}H_{10}ON_5Cl_2$	351	246	72	15
3c	$C_{14}H_{10}ON_5Cl_2$	351	213	77	15
3d	$C_{14}H_{10}ON_5Cl_2$	351	241	79	15
3e	$C_{14}H_{11}ON_5Br$	361	235	73	13
3f	$C_{19}H_{13}ON_5Cl$	362.5	215	80	10
3g	$C_{15}H_{13}O_2N_5Cl$	330.5	228	80	14

Synthesis of (5-amino-3-phenyl-1H-pyrazol-1-yl) (6-chloropyrzin-2-yl) methanone (3a):

IR (KBr) cm^{-1}: 3444 (N-H), 1692 (C=O),1640 (C=N), 909 (C-H)
^{1}H-NMR (300 MHz, DMSO-d_6): 8.50 (s,1H, py-H_5), 8.40 (s,1H,py-H_3), 8.00-8.20 (m,5H,Ar-H), 6.71(s, 2H, NH_2), 5.79 (s, 2H, CH_2).

Synthesis of (5-amino-3-(4-chloro)-1H-pyrazol-1-yl) (6-chloropyrazin-2-yl) methanone (3d):

IR (KBr) cm^{-1}: 3444 (N-H), 1690 (C=O),1642 (C=N), 910 (C-H)
^{1}H-NMR (300 MHz, DMSO-d_6): 8.50 (s, 1H, py-H_5), 8.40 (s, 1H, py-H_3), 8.01-8.20 (m, 4H, Ar-H), 6.71(s, 2H, NH_2), 5.79 (s, 2H, CH_2).

Synthesis of (5-amino-3-4-methoxy)-1H-pyrazol-1-yl) (6-chloropyrazin-2-yl)methanone(3g):

IR (KBr) cm^{-1}: 3444 (N-H), 1722 (C=O),1640 (C=N), 909 (C-H)
^{1}H-NMR (300 MHz, DMSO-d_6): 8.50 (s, 1H, py-H_5), 8.40 (s,1H,py-H_3),8.01-8.20 (m, 4H, Ar-H), 6.71(s, 2H, NH_2), 5.79 (s, 2H, CH_2), 3.94 (s, 3H, OCH_3).

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