



Research Article

Microwave Assisted Synthesis and antimicrobial activities of some 3-[4'-(4''-nitrophenoxy)-phenyl] -5-(substituted aryl)-2-pyrazoline-1- thiocarboamides

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ABSTRACTS

Some new 3-[4'-(4''-nitrophenoxy)-phenyl]-5-(substituted aryl)-2-pyrazoline-1-thiocarboamides have been synthesized employing microwave heating technique and evaluated for their antimicrobial activities. Substituted acetophenones were reacted with appropriately substituted benzaldehydes in presence of base to furnish substituted 4'-(4''-nitrophenoxy) chalcones (1a-f). These chalcones on further treatment with thiosemicarbazide in presence of potassium carbonate under microwave irradiation yielded the title compounds (2a-f). The structure of the newly synthesized compounds (2a-f) has been confirmed by suitable analytical and spectral analysis (IR, ¹H-NMR and MASS). All the compounds were screened for their antibacterial and antifungal activities in vitro.

Keywords: Microwave irradiation, 2-pyrazoline, thiosemicarbazide, antibacterial.

INTRODUCTION

The dihydro derivative of pyrazole is known as pyrazoline. Pyrazolines are well known nitrogen containing five membered heterocyclic compounds. Pyrazolines and their derivatives have been found to possess a variety of significant and diverse chemical and pharmacological activities such as antibacterial¹⁻³, antifungal⁴⁻⁵, antiviral⁶, antitubercular⁷⁻⁸, antidepressant⁹⁻¹⁰, antiamebic¹¹⁻¹², antiinflammatory¹³, anticonvulsant¹⁴, analgesic¹⁵ and anticancer¹⁶ activity. Pyrazolines are useful materials in drug research and are used extensively as useful synthon in organic synthesis¹⁷⁻²⁰. Keeping these facts in mind and in continuation of our research work on the synthesis of biological active heterocyclic compounds²¹⁻²³, it was planned to synthesize some new 2-pyrazoline derivatives in the present investigation. In the last few years Microwave Induced Organic Reaction Enhancement (MORE) chemistry has gained popularity as a non conventional technique for rapid organic synthesis²⁴, large number of reports have appeared in literature proving the synthetic utility of MORE-Chemistry²⁵⁻²⁶. Recently reported studies on the microwave irradiation for the synthesis of heterocyclic compounds revealed that it is safe, rapid, economical easy and eco-friendly method for chemical synthesis. Pollution free synthesis, shorter reaction time, easy work-up and minimum use of solvent are the major advantages of this technique²⁷. In this way targeting the preparation of the above mentioned nitrogen containing heterocycles, we report here in the synthesis of some

novel 3-[4'-(4''-nitrophenoxy)-phenyl]-5-(substituted aryl)-2-pyrazoline-1-thiocarboamides (2a-f). Substituted 4'-(4''-nitrophenoxy) chalcones were treated with thiosemicarbazide using anhydrous potassium carbonate under microwave irradiation (MWI) resulting in the formation of the title compounds (2a-f). The progress of the reaction was monitored by TLC using silica gel-G as adsorbent and benzene-ethyl acetate (9:1 v/v) as the eluent. The structure of the newly synthesized compounds were confirmed by elemental and spectral data (IR, ¹H-NMR and MASS) which are summarized in **Table I & II** respectively.

Table I: Physical data of newly synthesized compounds 3-[4'-(4''-nitrophenoxy)-phenyl]-5-(substituted aryl)-2-pyrazoline-1-thiocarboamides (2a-f).

| S.No. | Compound | R | Mol. formula (mol.wt.) | M.P. (°C) | Yield (%) | Reaction Time (MWI) | R _f value | % N | |
|-------|----------|--|--|--------------|--------------|---------------------------|-------------------------|--------|-------|
| | | | | | | (min.) | | Calcd. | Found |
| 1 | 2a | H | C ₂₂ H ₁₈ N ₄ O ₃ S (418) | 105 | 65 | 5.0 | 0.74 | 13.39 | 13.01 |
| 2 | 2b | 4-N-(CH ₃) ₂ | C ₂₄ H ₂₃ N ₅ O ₃ S (461) | 120 | 68 | 5.5 | 0.73 | 15.18 | 14.99 |
| 3 | 2c | 4-Cl | C ₂₄ H ₁₇ N ₄ O ₅ SCl (452.5) | 115 | 70 | 5.0 | 0.71 | 12.37 | 12.10 |
| 4 | 2d | 3,4-(OCH ₃) ₂ | C ₂₄ H ₂₂ N ₅ O ₅ S (478) | 90 | 71 | 6.5 | 0.70 | 14.64 | 14.08 |
| 5 | 2e | 4-OCH ₃ | C ₂₃ H ₂₀ N ₄ O ₄ S (448) | 110 | 69 | 6.5 | 0.72 | 12.5 | 11.98 |
| 6 | 2f | 3,4,5-(OCH ₃) ₃ | C ₂₅ H ₂₄ N ₄ O ₆ S (508) | 118 | 74 | 7.0 | 0.68 | 11.02 | 10.85 |

EXPERIMENTAL

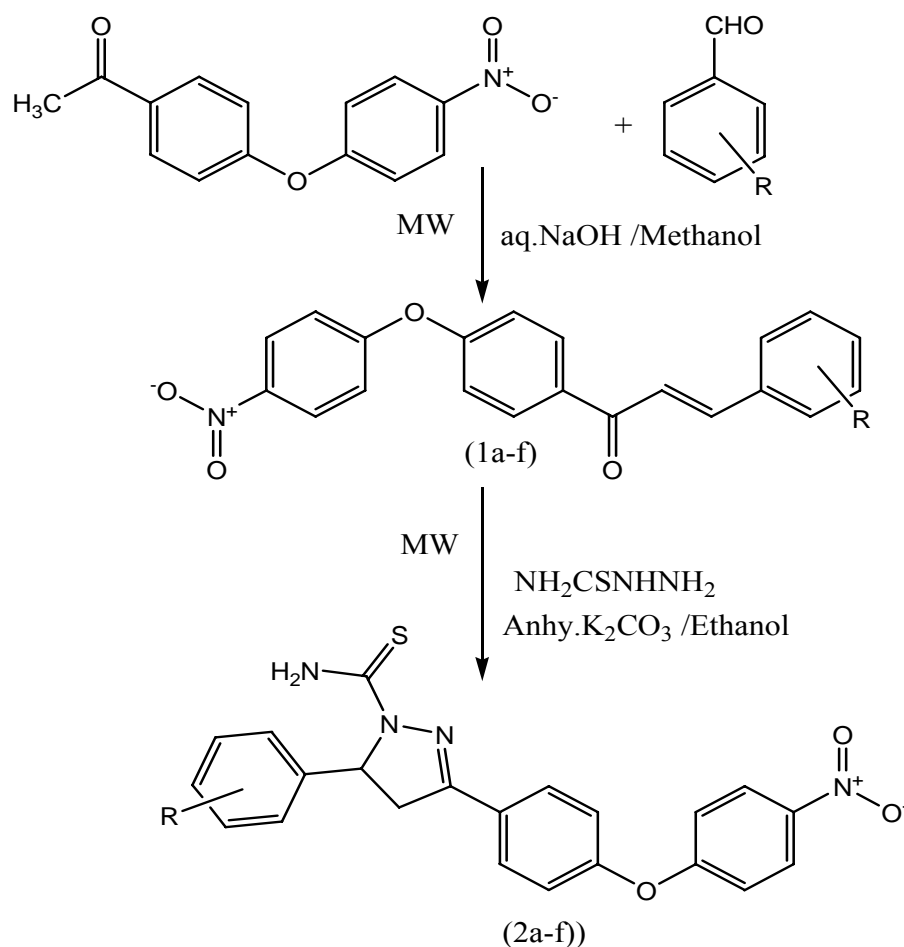
Starting materials and reagents were procured from commercial chemical suppliers. All the chemicals and solvents used were of laboratory grade. Melting points were determined in open capillaries and are uncorrected. The purity of compounds was checked by TLC on silica gel-G using benzene-ethyl acetate (9:1v/v) as the eluent. The IR spectra were recorded on Shimadzu FT-IR spectrophotometer using KBr (cm⁻¹). ¹H-NMR spectra were recorded on Bruker-DRX-600 spectrometer using TMS as internal standard and CDCl₃ or DMSO-d₆ as solvent. Mass spectra were obtained on an Agilent 6520-QTOF LCMS having an ESI source in positive mode. All the transformations were carried out in a domestic microwave oven Samsung 30N with power output 600 watts.

General procedure for the synthesis of substituted 4'-(4''-nitrophenoxy) chalcones (1a-f): A solution of 4-(4'-nitrophenoxy) acetophenone (0.01 mole) and variously substituted aryl aldehyde (0.01 mole) in methanol (15 ml) were taken in a conical flask, then added aq. Sodium hydroxide (40%, 15 ml) and the reaction mixture was irradiated under microwave irradiation for 3-4 minutes at 300 watts. The progress of the reaction was monitored

by TLC on silica gel-G using benzene-ethyl acetate (9:1 v/v) as the eluent. After completion of the reaction, the reaction mixture was cooled at room temperature then poured into ice cold water, neutralized with dil.HCl. The solid

obtained was filtered, washed with water, dried and recrystallized from alcohol and benzene to give products (1a-f)

General procedure for the synthesis of 3-[4'-(4''-nitrophenoxy)-phenyl]-5-(substituted aryl)-2-pyrazoline-1-thiocarboamides (2a-f): A mixture of the substituted 4'-(4''-nitrophenoxy) chalcone (1a-f, 0.01 mole) and thiosemicarbazide (0.01 mole) was dissolved in ethanol (5ml), then anhydrous K_2CO_3 (4.0g) added and stirred vigorously. After five min., the solvent was removed under vacuum and the dry powder was irradiated under microwave irradiation for 5-7 minutes at 600 watts. After completion of the reaction as followed by TLC examination, chilled water was added to the reaction mixture. The solid mass separated, which was filtered. It was washed with water, dried and recrystallized from methanol to afford pale yellow crystals as product (2a-f) in 65-80% yield **Scheme-I**.



R = (a) H, (b) 4-N-(CH₃)₂, (c) 4-Cl, (d) 3,4-(OCH₃)₂, (e) 4-OCH₃, (f) 3,4,5-(OCH₃)₃

Scheme-I.

Table II: Spectral data of synthesized compounds 3-[4'-(4''-nitrophenoxy)-phenyl]-5-(substituted aryl)-2-pyrazoline-1-thiocarboamides (2a-f).

| S.No.1 | Name of Compound | 3-[4'-(4''-nitrophenoxy)-phenyl]-5-(4-N,N'-dimethylamino phenyl)-2-pyrazoline-1-thiocarboamide (2b). |
|--------|---|--|
| 2b | IR (KBr, cm ⁻¹) | 3263 (N-H str.), 3061 (Ar-C-H str.), 2914 (C-H str.), 1548-1423 (C=C & C=N str.), 1240 (C=S str.) |
| | ¹ H-NMR(CDCl ₃ , δ ppm) | δ 8.98 (s, 2H, NH ₂), δ 3.01-3.34 (dd, 1H, H _a), δ 3.63-3.88 (dd, 1H, H _b), δ 5.92-6.01 (dd, 1H, H _x), δ 6.68-8.26 (m, 12H, Ar-H) |
| | Mass (FAB, m/z) | [M ⁺] 461 |
| S.No.2 | Name of Compound | 3-[4'-(4''-nitrophenoxy)-phenyl]-5-(4-chloro phenyl)-2-pyrazoline-1-thiocarboamide (2c). |
| 2c | IR (KBr, cm ⁻¹) | 3275 (N-H str.), 3057 (Ar-C-H str.), 2920 (C-H str.), 1589-1496 (C=C & C=N str.), 1242 (C=S str.) |
| | ¹ H-NMR(CDCl ₃ , δ ppm) | δ 8.98 (s, 2H, NH ₂), δ 3.31-3.41 (dd, 1H, H _a), δ 3.76-3.82 (dd, 1H, H _b), δ 5.94-6.02 (dd, 1H, H _x), δ 6.70-8.29 (m, 12H, Ar-H) |
| | Mass (FAB, m/z) | [M ⁺] 452.5 |
| S.No.3 | Name of Compound | 3-[4'-(4''-nitrophenoxy)-phenyl]-5-(3,4-dimethoxy phenyl)-2-pyrazoline-1-thiocarboamide (2d). |
| 2d | IR (KBr, cm ⁻¹) | 3286 (N-H str.), 3076 (Ar-C-H str.), 2918 (C-H str.), 1583-1440 (C=C & C=N str.), 1246 (C=S str.) |
| | ¹ H-NMR(CDCl ₃ , δ ppm) | δ 8.96 (s, 2H, NH ₂), δ 3.16-3.27 (dd, 1H, H _a), δ 3.64-3.87 (dd, 1H, H _b), δ 3.97 (s, 6H, OCH ₃), δ 5.94-6.03 (dd, 1H, H _x), δ 6.69-8.11 (m, 11H, Ar-H) |
| | Mass (FAB, m/z) | [M ⁺] 478 |
| S.No.4 | Name of Compound | 3-[4'-(4''-nitrophenoxy)-phenyl]-5-(4-methoxy phenyl)-2-pyrazoline-1-thiocarboamide (2e). |
| 2e | IR (KBr, cm ⁻¹) | 3290 (N-H str.), 3051 (Ar-C-H str.), 2920 (C-H str.), 1595-1473 (C=C & C=N str.), 1244 (C=S str.) |
| | ¹ H-NMR(CDCl ₃ , δ ppm) | δ 8.98 (s, 2H, NH ₂), δ 3.30-3.33 (dd, 1H, H _a), δ 3.69-3.78 (dd, 1H, H _b), δ 3.81 (s, 3H, OCH ₃), δ 5.89-6.02 (dd, 1H, H _x), δ 6.76-8.18 (m, 12H, Ar-H) |
| | Mass (FAB, m/z) | [M ⁺] 448 |
| S.No.5 | Name of Compound | 3-[4'-(4''-nitrophenoxy)-phenyl]-5-(3,4,5-trimethoxy phenyl)-2-pyrazoline-1-thiocarboamide (2f). |
| 2f | IR (KBr, cm ⁻¹) | 3340 (N-H str.), 3066 (Ar-C-H str.), 2928 (C-H str.), 1585-1462 (C=C & C=N str.), 1230 (C=S str.) |
| | ¹ H-NMR(CDCl ₃ , δ ppm) | δ 8.94 (s, 2H, NH ₂), δ 3.15-3.22 (dd, 1H, H _a), δ 3.68-3.85 (dd, 1H, H _b), δ 3.95 (s, 9H, OCH ₃), δ 5.94-6.03 (dd, 1H, H _x), δ 6.40-7.74 (m, 10H, Ar-H) |
| | Mass (FAB, m/z) | [M ⁺] 508 |

RESULT AND DISCUSSION

Our approach to the synthesis of target molecules started from preparation of chalcones. The chalcones were prepared in the presence of base by Claisen-Schmidt condensation of substituted acetophenones and aldehydes under microwave irradiation. The substituted 3-[4'-(4''-nitrophenoxy)-phenyl]-5-(substituted aryl)-2-pyrazoline-1-thiocarboamides (2a-f) were prepared by condensation of substituted 4'-(4''-nitrophenoxy) chalcones (1a-f) and

thiosemicarbazide in presence of catalytic amount of anhydrous K_2CO_3 under microwave irradiation. The synthetic procedure for preparation of title compounds is given in **Scheme-I**. The assigned structure and molecular formula of the newly synthesized compounds (2a-f) were confirmed on the basis of their elemental and spectral analysis (IR, 1H -NMR and MASS). The compounds were screened in vitro for their antibacterial and antifungal activities by disc diffusion assay against selected pathogenic bacteria and human pathogenic fungi. All the synthesized compounds exhibited moderate antibacterial and significant antifungal activities. The results of anti bacterial and antifungal activities expressed in term of Zone of inhibition in mm are reported in **Table III** as given below.

Antimicrobial Activity: All the compounds were screened for their antibacterial activities against E.coli, K.pneumoniae, B.Subtilis, Pseudomonas and antifungal activities against C.albicans and Aspergillus Fumigatus in vitro at a concentration 250 μ g/ml. Standard drug were used Ciprofloxacin and Fluncazole respectively. The Biological screening results expressed in term of zone of inhibition (mm) are tabulated in **Table III**.

Table III: - Biological screening results of compounds (2a-f), zone of inhibition (mm)

| Compound | Antibacterial activity | | | | Antifungal activity | |
|---------------|------------------------|--------------|----------|-------------|---------------------|--------------|
| | E.coli | K.pneumoniae | Bacillus | Pseudomonas | C.albicans | A. Fumigatus |
| 2a | 7 | 8 | 5 | 11 | 4 | 4 |
| 2b | 9 | 8 | 6 | 11 | 0 | 9 |
| 2c | 17 | 10 | 6 | 22 | 7 | 0 |
| 2d | 16 | 8 | 1 | 23 | 0 | 8 |
| 2e | 18 | 8 | 7 | 21 | 0 | 6 |
| 2f | 19 | 12 | 5 | 22 | 14 | 5 |
| Ciprofloxacin | 17 | 16 | 15 | 20 | - | - |
| Fluncazole | - | - | - | - | 10 | - |

CONCLUSION

All the transformations were carried out in domestic microwave oven. The use of microwave irradiation technique leads to considerable saving in the reaction time and is energetically profitable. The reaction under MWI is clean, efficient, eco-friendly, economically easy with shorter reaction time and integral part of green chemistry. The structure of the newly synthesized compounds was confirmed by their spectral data (IR, PMR and MASS) and some compounds were found to have promising antimicrobial activities.

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