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Microwave-Assisted Synthesis, Characterization and Antimicrobial Activity of Some Pyrazole Derivatives

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ABSTRACT

Reaction of 3-[4-(dimethylamino)phenyl]-(1-methyl/phenyl)prop-2-en-1-one (Chalcones) was carried out with hydrazine hydrate, phenyl hydrazine, isoniazide, nicotinic hydrazide and thiosemicarbezide (corresponding hydrazides) in ethanol containing a few drops of glacial acetic acid under microwave irradiation giving N, N-dimethylaniline containing pyrazole derivatives. The structures of the synthesized compounds were assigned on the basis of elemental analysis, IR and ^{1}H NMR. All the synthesized compounds have been screened for their antibacterial and antifungal activities.

Keywords: 3-[4-(dimethylamino) phenyl]-(1-methyl/phenyl)prop-2-en-1-one, Antimicrobial activity, Microwave irradiation.

INTRODUCTION

Microwave-assisted organic synthesis has opened up new opportunities for the synthetic chemists by providing novel routes not practical by conventional methods. Microwave-assisted synthesis is an eco-friendly and efficient method of synthesis of organic compounds as compared to the conventional method of synthesis. In this method, reaction occurs more rapidly, safely and with higher chemical yields and therefore, this method becomes superior to the conventional method. The conventional method, requiring a longer reaction time and larger quantities of solvents and reagents, causes environmental pollution and contributes to the health hazards.

Pyrazoles and their substituted derivatives are important biological agents. These are used as antitumor, antibacterial and antifungal, antiviral, antiparasitic, anti-tubercular and insecticidal agents. [1-10] Some of these compounds have also shown anti-inflammatory, anti-diabetic, anesthetic and analgesic properties. [11-14]

A microwave- assisted synthesis of α, β- unsaturated ketones (chalcones) was achieved by base catalysed aldol condensation of ketone with p-dimethylamimobenzaldehyde in the presence of piperidine [15], which undergo a subsequent cyclization reaction with various hydrazines affording pyrazoles. [16-18]

MATERIALS AND METHODS

The melting points were determined in open capillary tube and are uncorrected. The IR spectra were recorded on Perkin-Elmer 157 spectrometer using KBr pellets. The ^{1}H NMR spectra were scanned on a DRX-300 MHz spectrometer (300 MHz) in $CDCl_3$/DMSO-d_6 using TMS as internal standard and chemical shifts are expressed in δ ppm. Purity of synthesized compounds was checked by TLC using silica gel-G. Spots were exposed in an iodine chamber.

General Procedure for Preparation of chalcone (1a-b)

A convenient route for the synthesis of *α*, *β*-unsaturated ketones (Chalcone) was achieved by the reaction of p-dimethylaminobenzaldehyde (0.005 mol) with different ketones (Acetone and acetophenone) (0.005 mol) in the presence of piperidine, under microwave irradiation at 5 sec intervals. The specific reaction time was kept 2 min and then the reaction mixture was cooled in crushed ice. Progress of the reaction was monitored by TLC method. The solid thus obtained was filtered, washed with water, dried and purified by recrystallization from ethanol

Synthesis of 4-[4-(dimethylamino) phenyl] but-3-en-2-one (1a): Orange Crystal, Yield 89%, m.p. 145°C; IR (KBr) cm^{-1}: 1178 (-C-N); 1630 (-C=O); 2925-2948 (-CH_3), ^{1}H NMR (DMSO d_6) δ: 2.35 (3H, CH_3); 2.79 (6H, 2CH_3). Anal. Calcd. for $C_{12}H_{15}NO$: C, 76.16; H, 7.99; N, 7.40% Found: C, 76.01; H, 7.76; N, 7.30%.

Synthesis of 3-[4-(dimethylamino)phenyl]-1-phenylprop-2-en-1-one (1b): Red Crystal, Yield 85%, m.p.125°C; IR (KBr) cm^{-1}: 1165 (-C-N); 1651 (C=O); 2945 (-CH_3), ^{1}H NMR (DMSO d_6) δ: 2.75 (6H, 2CH_3); 6.54-7.81 (Ar-H); Anal. Calcd. for $C_{17}H_{17}NO$: C, 81.24; H, 6.82; N, 5.57%.

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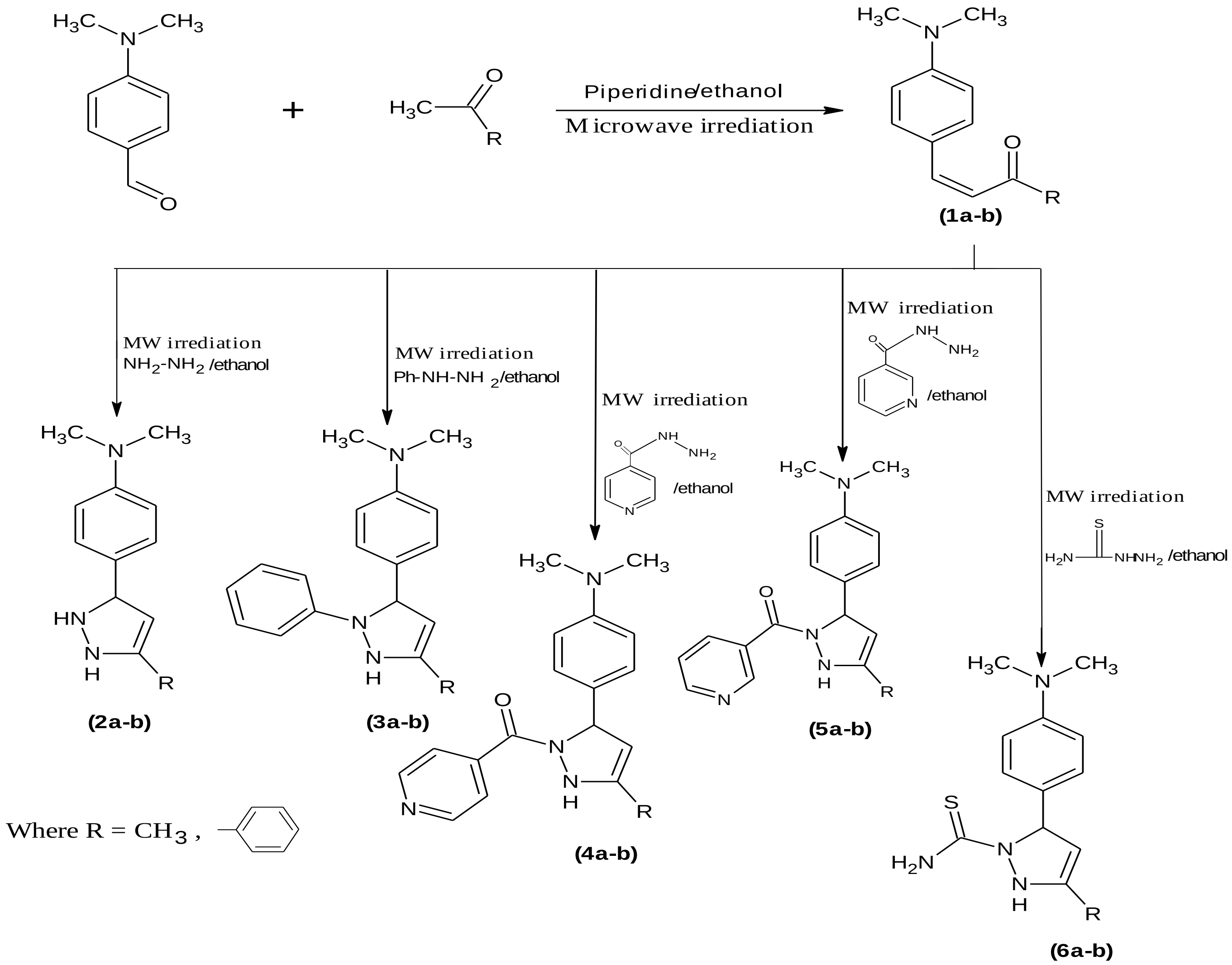

Scheme1: Synthesis of compound (1a-b), (2a-b), (3a-b), (4a-b), (5a-b) and (6a-b)

Found: C, 81.02; H, 6.66; N, 5.49%.

General Procedure for Preparation of compound 2a-b,3a-b,4a-b,5a-b,6a-b: A solution of the chalcone (0.004 mol.) in ethanol (10 mL) with the appropriate amount of different Hydrazines (Hydrazin hydrate, phenyl hydrazine, isoniazide, nicotinic hydrazide and thiosemicarbezide) (0.004 mol) in glacial acetic acid (2 drop) was react under microwave irradiation for a specific time of 1 min. Then the reaction mixture was poured into crushed ice and kept overnight at room temperature. The solid, thus obtained was filtered, washed with water, dried and recrystallized from ethanol. The completion of reaction is monitored by TLC method (elient: CHCl$_3$-MeOH (7:3)).

Synthesis of *N,N*-dimethyl-4-(5-methyl-2,3-dihydro-1*H*-pyrazol-3-yl)aniline (2a): Yield 81%, m.p. 212°C ; IR (KBr) cm^{-1}: 3383, 3415 (N-H pyrazole); 3041 (–Ar-CH); 2948, 2973 (R-CH$_3$); ^{1}H NMR (DMSO d$_6$) δ: 9.96, 9.81 (2H, NH); 4.62 (N-CH); 6.63-6.94 (Ar-H); 2.81 (6H, 2CH$_3$); 1.75 (3H, CH$_3$); Anal. Calcd. for $C_{12}H_{17}N_3$: C, 70.90; H, 8.43; N, 20.67%. Found: C, 70.49; H, 8.28; N, 20.53%.

Synthesis of *N*, *N*-dimethyl-4-(5-phenyl-2,3-dihydro-1*H*-pyrazol-3-yl)aniline (2b): Yield 77%, m.p. 225°C; IR (KBr) cm^{-1}: 3381, 3413 (N-H pyrazole); 3043 (–Ar-CH); 2978 (N-CH$_3$); ^{1}H NMR (DMSO d$_6$) δ: 9.96, 9.72 (2H, NH); 4.65 (N-CH); 6.59-7.29 (Ar-H); 2.83 (6H, 2CH$_3$); Anal. Calcd. for $C_{17}H_{19}N_3$: C, 76.95; H, 7.22; N, 15.84%. Found: C, 75.91; H, 7.10; N, 16.05%.

Synthesis of *N,N*-dimethyl-4-(5-methyl-2-phenyl-2,3-dihydro-1*H*-pyrazol-3-yl)aniline (3a): Yield 84%, m.p. 235-237°C; IR (KBr) cm^{-1}: 3414 (-N-H pyrazole); 3040 (–Ar-CH); 2940, 2955 (R-CH$_3$); ^{1}H NMR (DMSO d$_6$) δ: 9.62 (-NH, pyrazole); 4.66 (N-CH); 6.46-7.25 (Ar-H); 2.84 (6H, 2CH$_3$); 1.74 (3H, CH$_3$); Anal. Calcd. for $C_{18}H_{21}N_3$: C, 77.38; H, 7.58; N, 15.04%. Found: C, 77.02; H, 7.34; N, 14.83%.

Synthesis of 4-(2,5-diphenyl-2,3-dihydro-1*H*-pyrazol-3-yl)-*N,N*-dimethylaniline (3b): ield 79%, m.p. 215°C; IR (KBr) cm^{-1}: 3410 (N-H pyrazole); 3045 (–Ar-CH); 2940 (N-CH$_3$); ^{1}H NMR (DMSO d$_6$) δ: 9.76 (NH, pyrazole); 4.66 (N-CH); 6.56-7.28 (Ar-H); 2.85 (6H, 2CH$_3$); Anal. Calcd. for $C_{23}H_{23}N_3$: C, 80.90; H, 6.79; N, 12.31%. Found: C, 80.70; H, 6.51; N, 12.08%.

Synthesis of {5-[4-(dimethylamino)phenyl]-3-methyl-2,5-dihydro-1*H*-pyrazol-1-yl} (pyridin-4-yl)methanone (4a): Yield 75%, m.p. 225-228°C; IR (KBr) cm^{-1}: 3413 (N-H pyrazole); 3058 (–Ar-CH); 2952, 2955 (R-CH$_3$), 1660 (C=O), 1595 (C=N); ^{1}H NMR (DMSO d$_6$) δ: 9.72 (NH, pyrazole); 5.49 (N-CH); 6.52-6.94 (Ar-H); 1.79 (3H, CH$_3$); Anal. Calcd. For $C_{18}H_{20}N_4O$: C, 70.11; H, 6.54; N, 18.17%. Found: C, 70.00; H, 6.34; N, 18.08%.

Synthesis of {5-[4-(dimethylamino)phenyl]-3-phenyl-2,5-dihydro-1*H*-pyrazol-1-yl} (pyridin-4-yl)methanone (4b): Yield 82%, m.p. 231-233°C; IR (KBr) cm^{-1}: 3424 (N-H pyrazole); 3058 (–Ar-CH); 2948 (N-CH$_3$); 1656 (C=O); 1598 (C=N); ^{1}H NMR (DMSO d$_6$) δ: 9.69 (NH, pyrazole); 5.56

(N-CH); 6.52-7.30 (Ar-H); 2.84 (N-CH$_3$); Anal. Calcd. for $C_{23}H_{22}N_4O$: C, 74.57; H, 5.99; N, 15.12%. Found; C, 74.38; H, 5.72; N, 15.06%.

Synthesis of {5-[4-(dimethylamino)phenyl]-3-methyl-2,5-dihydro-1*H*-pyrazol-1-yl} (pyridin-3-yl)methanone (5a): Yield 76%, m.p. 222-225°C; IR (KBr) cm^{-1}: 3425 (N-H pyrazole); 3055 (-Ar-CH); 2925, 2948 (R-CH$_3$); 1665 (C=O); 1598 (C=N); ^{1}H NMR (DMSO d$_6$) δ: 9.71 (NH, pyrazole); 5.52 (N-CH); 6.54-6.96 (Ar-H); 1.79 (3H CH$_3$); Anal. Calcd. for $C_{18}H_{20}N_4O$: C, 70.11; H, 6.54; N, 18.17%. Found: C, 70.01; H, 6.24; N, 18.08%.

Synthesis of {5-[4-(dimethylamino)phenyl]-3-phenyl-2,5-dihydro-1*H*-pyrazol-1-yl} (pyridin-3-yl)methanone (5b): Yield 82%, m.p. 227-229°C; IR (KBr) cm^{-1}: 3428 (N-H pyrazole); 3058 (–Ar-CH); 2942 (N-CH$_3$); 1658 (C=O); 1598 (C=N); ^{1}H NMR (DMSO d$_6$) δ: 9.69 (NH, pyrazole); 5.55 (N-CH); 6.53-7.30 (Ar-H); 2.84 (6H, 2CH$_3$). Anal. Calcd. for $C_{23}H_{22}N_4O$: C, 74.57; N, 15.12; H, 5.99; O, 4.32 %. Found: C, 74.20; N, 15.02; H, 5.75; O, 4.19 %.

Synthesis of 5-[4-(dimethylamino)phenyl]-3-methyl-2,5-dihydro-1*H*-pyrazole-1-carbothioamide (6a): Yield 82%, m.p. 235-236°C; IR (KBr) cm^{-1}: 3309 (NH$_2$), 3379 (N-H pyrazole); 3041 (-Ar-CH); 2937, 2948 (R-CH$_3$); 1245 (C=S); ^{1}H NMR (DMSO d$_6$) δ: 9.78 (NH, pyrazole); 7.34 (2H, NH$_2$); 4.64 (N-CH); 6.52-6.93 (Ar-H); 1.75 (3H, CH$_3$); 2.87 (6H, 2CH$_3$); Anal. Calcd. for $C_{13}H_{18}N_4S$: C, 59.51; N, 21.35; H, 6.91; S, 12.22 %. Found: C, 60.01; N, 21.18; H, 6.54; S, 12.05 %.

Synthesis of 5-[4-(dimethylamino)phenyl]-3-phenyl-2,5-dihydro-1*H*-pyrazole-1-carbothioamide (6b): Yield 84%, m.p. 245-247°C; IR (KBr) cm^{-1}: 3308 (NH$_2$), 3377 (N-H pyrazole); 3049 (-Ar-CH); 2936 (N-CH$_3$); 1241 (C=S); ^{1}H NMR (DMSO d$_6$) δ: 7.39 (2H, NH$_2$); 9.78 (NH, pyrazole); 4.65 (N-CH); 6.53-7.29 (Ar-H); 2.86 (N-CH$_3$); Anal. Calcd. for $C_{18}H_{20}N_4S$: C, 66.63; N, 17.27; H, 6.21; S, 9.88 %. Found: C, 66.43; N, 17.04; H, 6.05; S, 9.71 %.

RESULTS AND DISCUSSION

The starting compounds 3-[4-(dimethylamino)phenyl]-(1-methyl/phenyl)prop-2-en-1-one (chalcone) (**1a-b**) react with corresponding hydrazides in ethanol containing a few drops of glacial acetic acid under microwave irradiation to give (**2a-b**)-(**6a-b**), respectively.

The structure was established though IR and ^{1}H NMR spectral data. The IR spectra of (**2a-b),** exhibited absorption bands for primary amine (-NH) at 3381-3415 cm^{-1}, (–N-N) at 1245- 1248 cm^{-1} and (-C-N) at 1084-1085 cm^{-1}. The ^{1}H NMR spectra of these compound revealed signals at δ = 9.72 - 9.96 ppm for (-NH) ring proton, a singlet at δ = 4.62-4.65 ppm for (-N-CH) at pyrazole ring, a multiplet at δ = 6.63-7.29 ppm for the aromatic protons.

The IR of (**3a-b),** exhibited absorption bands for primary amine (-NH) at 3410-3414 cm^{-1} and (–N-N) at 1242-1243 cm^{-1} and (-C-N) at 1110-1119 cm^{-1}. The ^{1}H NMR spectra of these compound revealed signals at δ = 9.62- 9.76 ppm for (-NH) proton, a singlet at δ = 4.65-4.66 ppm for (-N-CH) at pyrazole ring and a multiplet at δ = 6.46-7.28 ppm for the aromatic proton.

The IR of (**4a-b),** exhibited absorption bands for primary amine (-NH) at 3413-3424 cm^{-1}, (-C=N) at 1595-1598 cm^{-1}, (-C=O) at 1656-1660, (–N-N) at 1242- 1245 cm^{-1} and (-C-N) at 1085-1122 cm^{-1}. The ^{1}H NMR spectra of these compound revealed signals at δ = 9.69-9.72 ppm for (-NH) ring proton, a singlet at δ = 5.49-5.56 ppm for (-N-CH) at pyrazole ring and a multiplet at δ = 6.52-7.30 ppm for the aromatic proton.

The IR of (**5a-b),** exhibited absorption bands for primary amine (-NH) at 3425-3428 cm^{-1}, (-C=N) at 1598 cm^{-1}, (-C=O) at 1658-1665, (–N-N) at 1242- 1245 cm^{-1} and (-C-N) at 1084-1121 cm^{-1}. The ^{1}H NMR spectra of these compound revealed signals at δ = 9.69-9.71 ppm for (-NH) proton, a singlet at δ = 5.52-5.55 ppm for (-N-CH) at pyrazole ring and a multiplet at δ = 6.54-7.31 ppm for the aromatic proton.

The IR of (**6a-b),** exhibited absorption bands for primary amine (-NH) at 3377-3379cm^{-1}, 3308-3309 cm^{-1} for (-NH$_2$), 1163-1168 cm^{-1} for (–C=S) and (–N-N) at 1241-1249 cm^{-1}. The ^{1}H NMR spectra of these compound revealed signals at δ = 9.78 ppm for (-NH) proton, a singlet at δ = 4.64-4.65 ppm for (-N-CH) at pyrazole ring and a multiplet at δ = 6.52-7.29 ppm for the aromatic proton.

Table 1: Antimicrobial activity of all the synthesized compounds

S. No.	**Minimal Bactericidal Concentration (MBC) (µg/mL)**			**Minimal fungicidal Concentrations (FBC) (µg/mL)**		
	Gram negative		**Gram positive**			
	E. coli	***P. aeruginosa***	***S. aureus***	***C. albicans***	***A. niger***	***A. clavatus***
2a	250	500	250	500	500	500
2b	500	500	500	250	500	500
3a	100	250	250	250	250	500
3b	100	250	100	100	250	250
4a	250	500	250	500	500	500
4b	250	500	500	250	250	500
5a	100	250	250	100	250	250
5b	100	250	100	100	100	100
6a	100	250	250	250	250	500
6b	100	250	100	100	250	250
S.D.	50	100	50	100	100	100

Antimicrobial Activity

All the compounds ie., (**2a-b), (3a-b), (4a-b), (5a-b)** and **(6a-b)** were tested for antibacterial activity against *Escherichia coli* (Gram -ve), *Staphylococcus aureus* (Gram +ve), *Pseudomonas aeruginosa* (Gram +ve) bacteria and antifungal activity against three fungal strains *Candida albicans*, *Aspergillus niger* and *Aspergillus clavatus*. Ampicillin and griseofulvin were used as standard drugs for antibacterial and antifungal activity, respectively.

Minimal Bactericidal Concentrations (MBC) and Minimal Fungicidal Concentration (MFC) were determined using Broth dilution method. Serial dilution for primary and secondary screening, material and method was followed as per NCCLS-1992 manual. [19]

A stock solution was prepared of each drug (2000µg/mL concentration). In primary screening 1000, 500, 250 and 125µg/mL concentrations of the synthesized drugs were taken. The synthesized drugs found active in this primary screening were further tested in a second set of dilution against all microorganisms. The drugs found active in primary screening were similarly diluted to obtain 100, 50, 25, 12.5, 6.250, 3.125 and 1.5625µg/mL concentrations. The standard drug used in the present study is ampicilin for evaluating antibacterial activity which showed (50, 50 and 100µg/mL MBC against *S. aureus, E. coli* and *P. aeruginosa*, respectively. Griseofulvin is used as the standard drug for antifungal activity, which showed 100µg/mL MFC against all the species, used for the antifungal activity. The results of antimicrobial and antifungal activities of our synthesized compounds are shown in Table 1.

This work demonstrates a rapid, efficient, safe and eco-friendly method for synthesis of some pyrazole derivatives. All the compounds show good antimicrobial activity against all micro-organisms.

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