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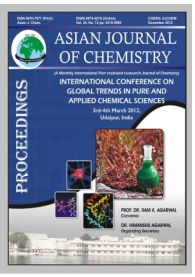

Solvent Free Synthesis of Different Substituted Pyrazoles Under Microwave Irradiation *via* One Pot Synthesis and their Biological Evaluation†

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Pyrazoles and their derivative are widely used as pharmaceutical and agrochemical agents and consequently a large number of synthetic routes to pyrazole have been reported. Due to the property of reducing blood sugar by pyrazole, it has resulted in the synthesis of their several congerers. In present study, we have synthesized set ot these pyrazoles by condensation of different substituted chalcones with hydrazine hydrate and DMSO/I_2 under microwave irradiation. The purity was determined using TLC and melting points and structural elucidations were carried out by spectral (IR, ^{1}H NMR, Mass) studies. The synthesized compounds were also used for various biological screening.

Key Words: Chalcone, Pyrazole, Microwave irradiation, Hydrazine hydrate.

INTRODUCTION

Pyrazole derivatives are well known as analgesic, antipyretic, antiinflammatory, antidiabetics, antifedant[1-4], anticonvulsant[5], anticancer[6]. Insecticidal, miticidal and hypoglycemic activities of pyrazole have been reported[7-9]. Pinto[10] has also reported medicinal importances of pyrazole derivatives. Due to this variation in regiochemistry of pyrazoles at 3 and 5 positions, there is a significant interest in the preparation of 3,5-disubstituted(alkyl or aryl)pyrazoles[11].

In the last few years microwave-induced organic reaction enhancement (MORE) chemistry is gaining popularity as a non-conventional technique for rapid organic synthesis[12,13] and many researchers have described accelerated organic reactions and number of paper have appeared proving the synthetic utility of MORE chemistry in routine organic synthesis[14-16]. It can be termed as e-chemistry because it is easy, effective, economical and eco-friendly and is believed to be a step towards green chemistry.

EXPERIMENTAL

All melting points were determined in open capillaries and are uncorrected. IR spectra were recorded on Shimadzu spectrophotometer on KBr plate. ^{1}H NMR was recorded by using Bruker F 113 V (400 MHz) NMR spectrometer DMSO as solvent and TMS as internal reference. Chemical shifts are expressed in d ppm. Mass spectral analysis was carried out on Shimadzu spectrometer. Experiments were performed using kenstar microwave oven with microwave energy output 900 W and frequency 2450 MHz.

Synthesis of 3,5- diarylpyrazole from chalcone

Microwave method A: Chalcone of 3 (1 mmol) was dissolved in 15 mL of DMSO in 250 mL conical flask capped with a funnel. To this was added hydrazine hydrate (5 mL, 80 % solution) dropwise with constant stirring at r.t. for 5min and the reaction mixture was irradiated inside the microwave oven at 30 % m.w. power (900 w) for 8-10 min. with short interruptions of 30-60 sec to avoid excessive evaporation of solvent. Progress of the reaction was monitored by TLC. The reaction mixture was cooled and poured into crushed ice (50 g) and extracted with ethyl acetate and washed with sodium thiosulphate and water to remove the iodine.

Classical method B: Compound **3** (1 mmol) was dissolved in 15 mL of DMSO in 250 mL R.B. flask attached with condenser and guard tube. To this was added hydrazine hydrate (5 mL, 80 % solution) drop wise with constant stirring at room temperature for 5 min. the formation of pyrazole was monitored by TLC and compared with co-TLC of authentic sample. Then, molecular iodine in catalytic amount was added to the reaction mixture and the mixture was further heated upto 130-40 ºC for 2 h. After the completion of the reaction mixture was cooled and poured into crushed ice (50 g) and extracted with ethyl acetate and washed with sodium thiosulphate and water to remove the iodine.

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Spectral data of synthesized compounds 4a-l

4a: 3-(Biphenyl-4-yl)-5-phenylpyrazole; IR (KBr, ν_{max}, cm^{-1}): 3332 (-NH str.), 1607 (C=N); ^1H NMR: δ 6.65 (s, 1H, C4-H), 7.37-7.88 (m, 14H, Ar-H), 11.14 (bs, 1H -NH, D_2O exchangeable). EI^+ *m/z*: 296 (M^+).

4b: 3-(Biphenyl-4-yl)-5-(4-methoxyphenyl)pyrazole; IR (KBr, ν_{max}, cm^{-1}): 3435 (-NH str.), 1603 (C=N); ^1H NMR: δ 3.83 (s,3H, $-OCH_3$), 6.76 (s, 1H, C4-H), 7.11-7.76 (m, 9H, Ar-H), 7.80 (d, 2H, *J* = 8.8 MHz, Ar-H), 7.05 (d, 2H, *J* = 9.2 MHz, Ar-H), 12.02 (bs, 1H, -NH, D_2 Oexchangeable). EI^+ *m/z*: 326 (M^+).

4c: 3-(Biphenyl-4-yl)-5-(3,4-dimethoxyphenyl)pyrazole; IR (KBr, ν_{max}, cm^{-1}): 3450 (-NH str.), 1647 (C=N); ^1H NMR: δ 3.51 (s, 6H, OCH_3), 6.80 (s, 1H, C4-H), 7.01-7.75 (m, 8H, Ar-H), 8.03 (d, 2H, *J* = 8 MHz), 7.73 (d, 2H, *J* = 8 MHz), 11.88 (bs, 1H, -NH, D_2O exchangeable). EI^+ *m/z*: 356 (M^+).

4d: 3-(Biphenyl-4-yl)-5-(3,4,5-trimethoxyphenyl) pyrazole; IR (KBr, ν_{max}, cm^{-1}): 3431 (-NH str.), 1637 (C=N); ^1H NMR: δ 3.94 (s, 9H, OCH_3), 6.86 (s, 1H, C4-H), 7.17-8.06 (m, 11H, Ar-H), 11.92 (bs, 1H, -NH, D_2O exchangeable). EI^+ *m/z*: 386 (M^+).

4e: 3-(Biphenyl-4-yl)-5-(4-bromophenyl)pyrazole; IR (KBr, ν_{max}, cm^{-1}): 3325 (NH str.), 1647 (C=N); ^1H NMR: δ 6.86 (s, 1H, C4-H), 7.31-8.03 (m, 13H, Ar-H), 11.86 (bs, 1H, -NH, D_2O exchangeable). EI^+ *m/z*: 374 (M^+).

4f: 4-[3-(biphenyl-4-yl)-pyrazole-5-yl]-*N,N*-dimethyl-aniline; IR (KBr, ν_{max}, cm^{-1}): 3430 (-NH str.), 1613 (C=N); ^1H NMR: δ 6.94 (s, 1H, C4-H), 7.02-7.73 (m, 9H, Ar-H),12.27 (bs, 1H, NH, D_2O exchangeable), 3.34 (s, 6H, $N(CH_3)_2$), 7.71 (d, 2H, *J* = 8.8 MHz, Ar-H), 7.28 (d, 2H, *J* = 8.4 MHz, Ar-H). EI^+ *m/z*: 342 (M^++2).

4g: 3-(Biphenyl-4-yl)-5-(3-nitrophenyl)pyrazole; IR (KBr, ν_{max}, cm^{-1}): 3333 (-NH str.), 1620 (C=N); ^1H NMR: δ 6.67 (s, 1H, C4-H), 7.17-8.06 (m, 13H, Ar-H), 11.88 (bs, 1H, NH, D_2O exchangeable). EI^+ *m/z*: 339 (M^+-2).

4h: 3-[2-Chloro-3-methyl-4-(methylsulfanyl)phenyl]-5-(4-methoxyphenyl)-1*H*-pyrazole; IR (KBr, ν_{max}, cm^{-1}): 3340 (-NH str.), 1637 (C=N); ^1H NMR: δ 6.89 (s, 1H, C4-H), 7.00-7.95 (m, 6H, Ar-H), 3.90 (s, 3H, OCH_3), 2.07 (s, 3H, CH_3), 2.56 (s, 3H, SCH_3), 11.77 (bs, 1H, NH, D_2O exchangeable). EI^+ *m/z*: 344 (M^+).

4i: 3-[2-Chloro-3-methyl-4-(methylsulfanyl)phenyl]-5-(3,4-dimethoxyphenyl)-1*H*-pyrazole; IR (KBr, ν_{max}, cm^{-1}): 3351 (-NH str.), 1635 (C=N); ^1H NMR: δ 6.85 (s, 1H, C4-H), 7.00-7.40 (m, 5H, Ar-H), 3.99 (s, 3H, OCH_3), 2.07 (s, 3H, CH_3), 2.64 (s, 3H, SCH_3), 12.68 (bs, 1H, NH, D_2O exchangeable). EI^+ *m/z*: 375 (M^+-1).

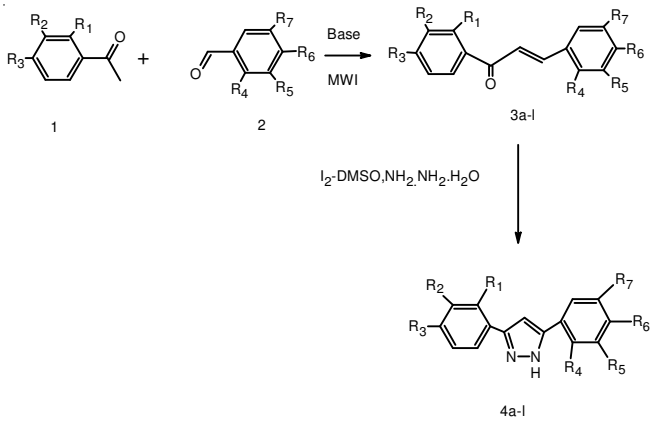
4j: 3-[2-Chloro-3-methyl-4-(methylsulfanyl)phenyl]-5-(3,4,5-trimethoxyphenyl)-1H-pyrazole; IR (KBr, ν_{max}, cm^{-1}): 3378 (-NH str.), 1618 (C=N); ^1H NMR: δ 6.79 (s, 1H, C4-H), 7.05-7.28 (m, 3H, Ar-H), 3.94 (s, 3H, OCH_3), 2.06 (s, 3H, CH_3), 2.63 (s, 3H, SCH_3), 12.80 (bs, 1H, NH, D_2O exchangeable). EI^+ *m/z*: 405 (M^++1).

4k: 3-[2-Chloro-3-methyl-4-(methylsulfanyl)phenyl]-5-(2,4-dichlorophenyl)-1H-pyrazole; IR (KBr, ν_{max}, cm^{-1}): 3420 (-NH str.), 1601 (C=N); ^1H NMR: δ 6.98 (s, 1H, C4-H), 7.00-7.38 (m, 5H, Ar-H), 2.33 (s, 3H, CH_3), 2.51 (s, 3H, SCH_3), 12.13 (bs, 1H, NH, D_2O exchangeable). EI^+ *m/z*: 384 (M^++3).

4l: 5-(4-Bromophenyl)-3-[2-chloro-3-methyl-4-(methylsulfanyl)phenyl]-1H-pyrazole; IR (KBr, ν_{max}, cm^{-1}): 3351 (-NH str.), 1635 (C=N); ^1H NMR: δ 6.67 (s, 1H, C4-H), 7.06-8.87 (m, 7H, Ar-H), 2.07 (s, 3H, CH_3), 2.64 (s, 3H, SCH_3), 12.30 (bs, 1H, NH, D_2O exchangeable). EI^+ *m/z*: 395 (M^+-2).

RESULTS AND DISCUSSION

As a result of present studies related to the development of synthetic protocols using microwave irradiation, we report a novel and easy access to 3,5-diaryl pyrazole using a one pot procedure and demonstrate its superiority over previously reported classical heating method. We report in this paper some Clasien-Schmidt condensation reaction between substituted acetophenone (1) and substituted benzaldehyde (2) in the presence of base to give intermediate chalcones **3a-l**, which undergo a rapid cyclization with hydrazine hydrate and I_2-DMSO under microwave irradiation at 30 ºC to yield 3-5-arylated pyrazole **4a-l** quantitatively in 8-10 min (**Scheme-I**).



Scheme-I

TABLE-1
SYNTHESIZED 3,5-diaryl-pyrazoles **4a-l**

Comp. no.	R_1	R_2	R_3	R_4	R_5	R_6	R_7
4a	H	H	C_6H_5	H	H	H	H
4b	H	H	C_6H_5	H	H	OCH_3	H
4c	H	H	C_6H_5	H	OCH_3	OCH_3	H
4d	H	H	C_6H_5	H	OCH_3	OCH_3	OCH_3
4e	H	H	C_6H_5	H	H	Br	H
4f	H	H	C_6H_5	H	H	$N(CH_3)_2$	H
4g	H	H	C_6H_5	H	NO_2	H	H
4h	Cl	CH_3	SCH_3	H	H	OCH_3	H
4i	Cl	CH_3	SCH_3	H	OCH_3	OCH_3	H
4j	Cl	CH_3	SCH_3	H	OCH_3	OCH_3	OCH_3
4k	Cl	CH_3	SCH_3	Cl	H	Cl	H
4l	Cl	CH_3	SCH_3	H	H	Br	H

The IR spectra of pyrazoles **4a-l** showed sharp absorption bands due to -NH stretching at 3450-3300 cm^{-1}. ^1H NMR spectra showed -NH peaks in the offset region of spectra and were D_2O exchangeable. Chemical shift of H-4 in pyrazoles was well distinguished in intramolecular hydrogen bonded pyrazoles.

Antimicrobial evaluation: The antimicrobial activity was determined using cup plate agar diffusion method by measuring the zone of inhibition in mm. All the newly synthesized compounds (**4a-l**) were screened *in vitro* for their antibacterial

TABLE-2
CHARACTERIZATION DATA OF 3,5-diaryl-pyrazole **4a-l**

Compd. no.	m.p. (ºC)	m.f. (m.w.)	Reaction time		Yields (%)	
			Microwave (min.)	Classical (h)	Microwave	Classical
4a	90	$C_{21}H_{16}N_2$ (296.13)	9	2	80	60
4b	100	$C_{22}H_{18}N_2O$ (326.14)	8	2	82	72
4c	150	$C_{23}H_{20}N_2O_2$ (356.15)	8	2	78	60
4d	105	$C_{24}H_{22}N_2O_3$ (386.16)	10	1.5	80	62
4e	165	$C_{21}H_{15}N_2Br$ (374.04)	8	2	84	59
4f	135	$C_{23}H_{21}N_3$ (339.17)	9	2	79	64
4g	130	$C_{21}H_{15}N_3O_2$ (341.12)	10	2	83	69
4h	90	$C_{18}H_{17}N_2OSCl$ (344.08)	10	1.5	80	61
4i	80	$C_{19}H_{19}N_2O_2SCl$ (374.09)	8	2	81	57
4j	110	$C_{20}H_{21}N_2O_3SCl$ (404.10)	8	2	88	72
4k	105	$C_{17}H_{13}N_2SCl_3$ (381.99)	9	2	85	67
4l	65	$C_{17}H_{14}N_2SBrCl$ (397.97)	10	1.5	86	56

TABLE-3
ANTIMICROBIAL ACTIVITY OF THE SYNTHESIZED COMPOUNDS 1-8 ZONE OF INHIBITION (mm)

Comp. no.	Antibacterial activity				Antifungal activity	
	B. subtilis	*P. areoginous*	*K. pneumoniae*	*E. coli*	*A. fumigatus*	*C. allbicans*
4a	11	22	16	20	17	14
4c	13	20	17	14	13	10
4d	14	18	18	18	17	10
4f	12	19	18	20	16	20
4h	15	11	10	14	13	13
4i	13	10	16	16	14	NA
4k	10	20	20	21	13	16
4l	13	13	16	19	13	NA
C_1	26	25	30	27	-	22

Standard drug for antibacterial activity C_1 ciprofloxacin; Standard drug for antifungal activity C_1 fluconazol

activity against four bacteria *viz. B. subtilis, K. pneumoniae, E. coli, P. aureoginosa* at a concentration of 500 µg/mL. Antifungal activity was tested against *Candida albicans* and *Aspergillus fumigates* at a concentration of 500 µg/mL. Ciprofloxacin (10 µg/disc) was used as a standard drug for antibacterial screening and fluconazole (10 µg/disc) was used as a standard for antifungal screening. The agar medium was purchased from HI Media Laboratories Ltd., Mumbai, India. Preparation of nutrient broth, subculture, base layer medium agar medium and peptone water was done as per the standard procedure.

The screening results indicate that compounds **4a, 4c, 4d, 4f, 4k** show promising activity against *K. pneumoniae, E. coli, P. aureoginosa* and poor activity against *B. subtilis*. While these compounds were moderate antifungal ativities. Compounds **4h, 4i, 4l** exhibited moderate antibacterial and antifungal activities. Each experiment was done in triplicate and the average reading was taken.

Conclusion

In summary, this work demonstrates a rapid, efficient and environmentally friendly method of synthesis of 3,5-diaryl pyrazoles under microwave heating and the results obtained confirm the superiority of the microwave irradiation method over the classical heating one.

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