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Note

Improved synthesis of chalcones and pyrazolines under ultrasonic irradiation

Ragini Gupta[a,*], Neetu Gupta[b] & Anshu Jain[a]

[a]Department of Chemistry, Malaviya National Institute of Technology, Jaipur 302 017, India

E-mail: raginigupta@mnit.ac.in

[b]Centre of Advanced Studies, Department of Chemistry, University of Rajasthan, Jaipur 302 004, India

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Five 1,3-diarylprop-2-en-1-ones **3a-e** are synthesized by Claisen-Schmidt condensation of aryl methyl ketones and 4-chlorobenzaldehyde to give pyrazolines **5a-e** by cyclization with phenylhydrazine in gl. acetic acid using ultrasonic irradiation in lesser time with higher yields. All the synthesized compounds are characterized by elemental analyses and spectral data IR, PMR and are screened for their antimicrobial activities. Some of them have shown promising results against *E. coli*, *S. aureus*, *C. albicans* and *A. niger*.

Keywords: Chalcones, 2-pyrazolines, Claisen-Schmidt condensation, sonochemistry, antimicrobial

Pyrazolines are well known important nitrogen containing five membered heterocyclic compounds. They possess a broad spectrum of biological activities *viz* antibacterial[1], antifungal[2], antitubercular[3], antitumor[4], antidepressant[5], anticonvulsant[6], insecticidal[7], antidiabetic[8], antiacetylcholinesterase[9], molluscicidal[10] and antinociceptive[11]. Pyrazolines are used extensively as useful synthons in organic synthesis[12-15]. Among various pyrazoline derivatives, 2-pyrazolines seem to be the most frequently studied pyrazoline type compounds. A classical synthesis of these compounds involves the base catalyzed Claisen-Schmidt condensation of aryl methyl ketones and aldehydes to give chalcones, which undergo a subsequent cyclization reaction with hydrazines affording 2-pyrazolines[16]. Now-a-days, application of ultrasound (sonochemistry) has become an exciting field of research. The chemical effects of ultrasound are diverse and include substantial improvements in both stoichiometric and catalytic chemical reactions. Ultrasonic irradiation accelerates the reactivity million fold and many synthetically useful reactions were successfully accomplished[17,18]. As compared to conventional conditions, *viz* strong base and long reaction time, the ultrasonic irradiation procedure is milder and more convenient leading to higher yields in shorter reaction time[19,20]. These observations stimulated us to synthesize bioactive compounds. To the best of our knowledge, there is no earlier report on the synthesis of 4,5-dihydro-3-aryl-5-(4-chlorophenyl)-*N*[1]-phenylpyrazoles by ultrasonication (**Scheme I**).

The title compounds were characterized by elemental analyses, melting points, IR, ^{1}H NMR measurements.

Materials and Methods

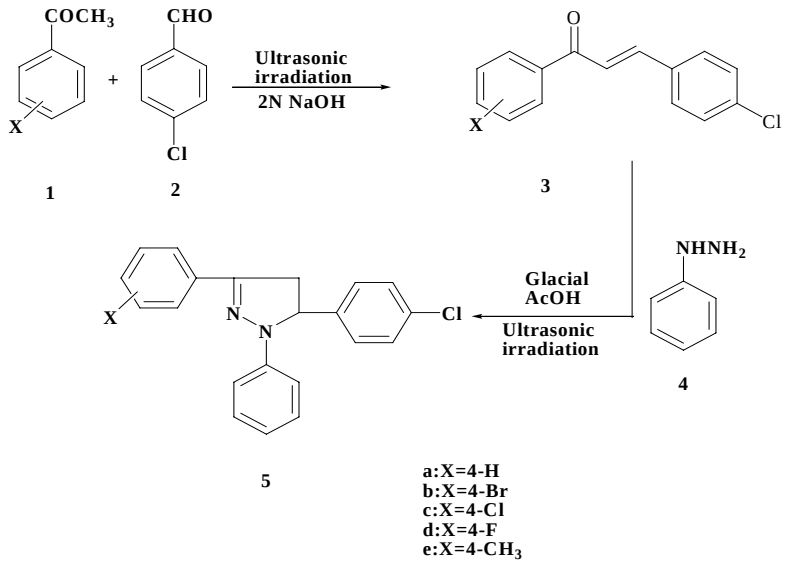
Fluorinated acetophenones were prepared by Buu-Hoi *et al.* method[21]. Aromatic aldehydes, phenylhydrazine, sodium hydroxide and gl. acetic acid, are all commercial products and were used as received without further purification. Chalcones[22] and pyrazolines[16] were prepared conventionally using literature methods.

Experimental Section

Melting points are uncorrected. IR spectra were recorded on a Perkin-Elmer Model-557 and Nicolet Magna Model-750 spectrometer on KBr pellets. ^{1}H NMR spectra were measured on Bruker DRX 300 NMR (300 MHz FT NMR) spectrometer using TMS as internal standard and $CDCl_3$ as solvent. Sonication was performed in a Toshniwal Model SW 4 ultrasonic-bath with a frequency of 37 KHz and a nominal power of 500 W. The reaction flask was located in the maximum energy area in the bath, and the addition or removal of water controlled the temperature of the water-bath.

Preparation of 1-aryl-3-(4´-chlorophenyl)-prop-2-en-1-ones 3a-e

4-Chlorobenzaldehyde (**2**, 2.5 mmole, 0.35 g), appropriate aryl methyl ketone (**1**, 2.5 mmole), 95% EtOH (20 mL) and 2*N* NaOH (3 mL) were taken into a 100 mL conical flask. The mixture was irradiated by an ultrasonic generator in a water-bath at 30-35°C for 2 min. The solid product so formed was diluted with water and neutralized with 2*N* HCl (3 mL). Then it



1 2 3 4 5

Scheme I

Table I — Synthesis of 4,5-dihydro-3-aryl-5-(4-chlorophenyl)-*N*[1]-phenylpyrazoles **5a-e** by using ultrasonic irradiation

Compd	X	Temperature (°C)	Time (min)	Yield (%)	Product m.p. (°C)
5a	4-H	25	30	80	133
5b	4-Br	30	40	84	120
5c	4-Cl	35	60	82	108
5d	4-F	32	70	86	110
5e	4-CH_3	40	100	90	155

was filtered, washed well with cold water (2 × 25 mL) and recrystallized from ethanol to afford yellow shiny crystals **3a-e**. Their physical characteristics and analytical data are given in **Table I**.

Preparation of 4,5-dihydro-3-aryl-5-(4-chlorophenyl)-*N*[1]-phenylpyrazoles 5a-e

1-Aryl-3-(4′-chlorophenyl)-prop-2-en-1-one **3a-e**, (2.5 mmole), phenylhydrazine **4**, (2.5 mmole) and gl. acetic acid (20 mL) were taken into a 100 mL conical flask. This reaction flask was suspended at the center of the ultrasonic cleaning-bath to get the maximum ultrasound energy and sonicated until crystals appeared or starting chalcone disappeared. The reaction-mixture was poured into crushed ice and left overnight. The precipitate was separated by filtration, washed well with water (2 × 25 mL), dried and recrystallized from ethanol to afford orange coloured crystals. The products were characterized by elemental analyses and IR, ^{1}H NMR spectral data. The time and temperature required for the formation of various pyrazolines is indicated in **Table I**.

Results and Discussion

High efficiency synthesis by ultrasonic irradiation

Synthesis of 2-pyrazolines **5a-e** was carried out in good yields by the reaction of chalcones **3a-e** with phenylhydrazine **4** catalyzed by gl. acetic acid under ultrasonic irradiation at 25-45°C within 25-150 min. It has been observed that in the conventional method[23], the mixture of chalcone **3a-e** phenylhydrazine and gl. acetic acid was refluxed at 30-40°C for 3-4 hr to produce 2-pyrazolines **5a-e** in 70% yield. However, when this reaction was performed under sonication the reaction goes rapidly within 30 minutes and yield was significantly improved to 80%.

The IR and ^{1}H NMR data of all the synthesized compounds are recorded in **Table II.**

The following sequence of reaction appears to afford a satisfactory explanation of the mode of formation of the products (**Scheme II**). This reaction involves the initial formation of an arylhydrazone with subsequent attack of nitrogen upon the carbon-carbon double bond.

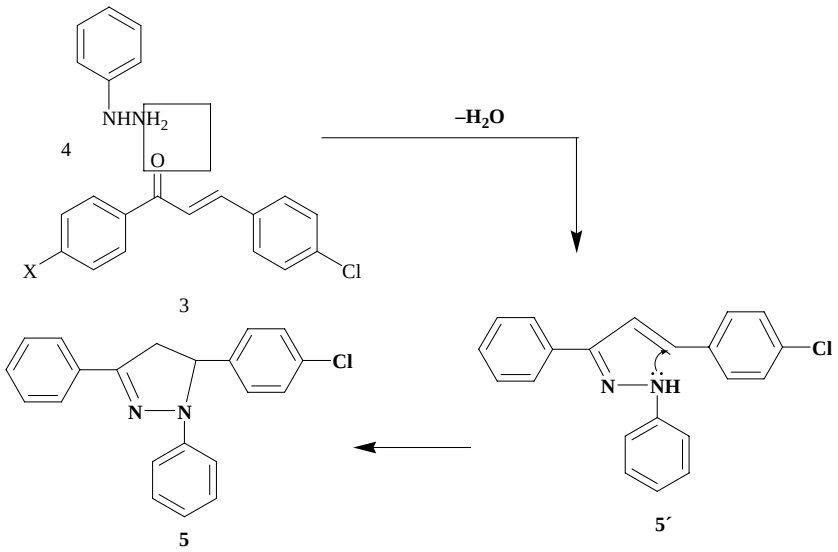
Antimicrobial Activity

All the synthesized compounds **5a-e** were screened for their antimicrobial activity against the Gram-negative bacteria *Escherichia coli*, Gram-positive bacteria *Staphylococcus aureus* and fungi *Candida*

albicans and *Aspergillus niger* at Ccompound **5b** shows good activity against *E. coli* at 800 and 200 ppm concentration. While compound **5d** shows comparable activity to Streptomycin at 800 and 400 ppm against *S. aureus*. Compounds **5b** and **5e** show good activity against *A. niger* at 800 and 400 ppm concentration while the activity of compound **5e** is comparable to standard value at 200 ppm concentration. Compound **5d** and **5c** show good activity against *C. albicans* at 800 and 400 ppm concentration while compound **5c** is even active at 200 ppm concentration. Detailed antimicrobial activity is tabulated in **Tables III** and **IV**.

Table II — Spectral data of 4,5-dihydro-3-aryl-5-(4-chlorophenyl)-N^1-phenylpyrazoles **5a-e**

Compd	IR, KBr, cm^{-1}	^1H NMR, δ, ppm ($CDCl_3$)
5a	3050 (aromatic C-H str), 2920 (aliphatic C-H str), 1620 (C=N str), 1580 (C=C str), 750 (C-Cl str)	3.01 (dd, *J* = 15.5, 6.1 Hz, 1H, CH_2 (Pyraz)), 3.65 (dd, *J* = 15.6, 11.5 Hz, 1H, CH_2 (Pyraz)), 5.38 (dd, *J* = 12.6, 7.1 Hz, 1H, CH (Pyraz)), 6.7-7.8 (m, ArH, 14H)
5b	3060 (aromatic C-H str), 2940 (aliphatic C-H str), 1610 (C=N str), 1570 (C=C str), 760 (C-Cl str), 540 (C-Br str)	3.20 (dd, *J* = 16.1, 5.6 Hz, 1H, CH_2 (Pyraz)), 3.78 (dd, *J* = 15.8, 11.6 Hz, 1H, CH_2 (Pyraz)), 5.42 (dd, *J* = 12.5, 7.0 Hz, 1H, CH (Pyraz)), 6.6-7.9 (m, ArH, 13H)
5c	3020 (aromatic C-H str), 2931 (aliphatic C-H str), 1600 (C=N str), 1580 (C=C str), 740 (C-Cl str)	3.25 (dd, *J* = 15.5, 6.1 Hz, 1H, CH_2 (Pyraz)), 3.64 (dd, *J* = 15.6, 11.5 Hz, 1H, CH_2 (Pyraz)), 5.40 (dd, *J* = 12.6, 7.1 Hz, 1H, CH (Pyraz)), 6.7-7.9 (m, ArH, 13H)
5d	3040 (aromatic C-H str), 2960 (aliphatic C-H str), 1610 (C=N str), 1570 (C=C str), 1240 (C-F str), 750 (C-Cl str)	3.24 (dd, *J* = 16.0, 6.4 Hz, 1H, CH_2 (Pyraz)), 3.76 (dd, *J* = 15.7, 11.5 Hz, 1H, CH_2 (Pyraz)), 5.46 (dd, J = 12.6, 7.1 Hz, 1H, CH (Pyraz)), 6.7-7.9 (m, ArH, 13H)
5e	3060 (aromatic C-H str), 2935 (aliphatic C-H str), 1620 (C=N str), 1580 (C=C str), 742 (C-Cl str)	2.3 (s, CH_3, 3H), 3.40 (dd, *J* = 15.7, 6.2 Hz, 1H, CH_2 (Pyraz)), 3.75 (dd, *J* = 15.8, 11.7 Hz, 1H, CH (Pyraz)), 5.46 (dd, *J* = 12.5, 7.0 Hz, 1H, CH_2 (Pyraz)), 6.6-8.0 (m, ArH, 16H)



Scheme II

Conclusion

In conclusion, we have found an efficient and convenient procedure for the preparation of 2-pyrazolines *via* the cyclization of chalcones and phenylhydrazine in gl. acetic acid under ultrasonic irradiation. It was observed that the electron donating group (CH_3) increases the rate of reaction as well as

Table III — Antibacterial activity of 4,5-dihydro-3-aryl-5-(4-chlorophenyl)-N^1-phenylpyrazoles **5a-e**

Compd	Mean value of area of inhibition in mm (800 ppm) IZ(AI)		Mean value of area of inhibition in mm (400 ppm) IZ(AI)		Mean value of area of inhibition in mm (200 ppm) IZ(AI)	
	S. aureus	*E. coli*	*S. aureus*	*E. coli*	*S. aureus*	*E. coli*
Streptomycin	12	10	10	08	7.8	6.2
5a	10 (0.83)	09 (0.90)	08 (0.80)	07 (0.87)	5.6 (0.72)	5.2 (0.83)
5b	09 (0.75)	11 (1.10)	6.6 (0.66)	8.9 (1.11)	4.1 (0.52)	7.0 (1.13)
5c	08 (0.07)	08 (0.80)	6.9 (0.69)	06 (0.75)	5.1 (0.65)	4.3 (0.69)
5d	11 (0.92)	08 (0.80)	09 (0.90)	07 (0.87)	6.7 (0.85)	4.2 (0.68)
5e	10 (0.83)	07 (0.70)	8.1 (0.81)	5.6 (0.70)	5.9 (0.76)	-

IZ = Inhibition area (zone) excluding diameter of disc
AI (Activity Index) = Inhibition area of sample / inhibition area of standard

Table IV— Antifungal activity of 4,5-dihydro-3-aryl-5-(4-chlorophenyl N^1-phenylpyrazoles **5a-e**

Compd	Mean value of area of inhibition in mm (800 ppm) IZ(AI)		Mean value of area of inhibition in mm (400 ppm) IZ(AI)		Mean value of area of inhibition in mm (200 ppm) IZ(AI)	
	C. albicans	*A. niger*	*C. albicans*	*A. niger*	*C. albicans*	*A. niger*
Ketoconazole	10	09	08	07	07	06
5a	09(0.90)	08 (0.89)	6.9 (0.86)	6.8 (0.97)	6.9 (0.98)	5.3 (0.88)
5b	06(0.60)	09 (1.0)	4.1 (0.51)	07 (1.0)	5.8 (0.83)	5.8 (0.97)
5c	11 (1.10)	08 (0.89)	09 (1.12)	5.9 (0.84)	7.8 (1.11)	4.7 (0.78)
5d	10 (1.0)	09 (1.0)	08 (1.0)	6.0 (0.86)	-	5.3 (0.88)
5e	07 (0.70)	12 (1.33)	5.9 (0.73)	9.3 (1.33)	4.8 (0.68)	06(1.0)

IZ = Inhibition area (zone) excluding diameter of disc
AI (Activity Index) = Inhibition area of sample / inhibition area of standard

its yield. Further, in the halogen series time required for pyrazoline formation increases as the electronegetivity of halogen atom increases, which is consistent with the trend obtained by Li J-T *et al*[25].

Compared to the classical methods, the main advantage of the present procedure is milder reaction conditions, higher yields and shorter reaction time period.

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