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Synthesis, characterization and antimicrobial activity of some 2-(propen-1-one) aryl 3-substituted phenothiazine

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ABSTRACT

1-(4-phenyl)-3-(4-hydroxyphenyl)-2-propen-1-one 1was prepared by condensation of 4-hydroxy benzaldehyde with acetophenone by Claisen-Schmidt Condensation. When 1-(4-phenyl)-3-(4-hydroxyphenyl)-2-propen-1-one combines with substituted anilines it gives 1-(4-phenyl)-3-(4'-aminophenyl) aryl-2-propen-1-one 2. When 2 undergo cyclization with sulphur and iodine gives 2-(propen-1-one) aryl-3-substituted phenothiazines 3. All these reactions are carried out under microwave irradiation in microwave oven. Chalcones (α,β) unsaturated aromatic ketone are important intermediate product in organic synthesis. Phenothiazine is an organic compound that occurs in various antipsychotic and antihistaminic drugs. The compound is related to the thaizine class of heterocyclic compounds. Derivatives of the parent compound find wide use as drugs. Application of microwave power system in the chemical synthesis of some phenothiazine derivatives is described. Heterocyclic ring formation, aromatic nucleophilic substitution and heterocyclic aldehydes or ketones condensation reactions were performed on solid support or under solvent free reaction conditions. Comparision of microwave assisted synthesis with the conventional synthetic methods demonstrates advantages related to shorter reaction times and in some cases better reaction yields. Structural elucidation of synthesized compounds has been made on the basis of elemental analysis, I.R. spectral studies and HNMR spectral studies. The antibacterial activity of these compounds have also been screened and found to be effective against gram + ve- and gram –ve bacteria

Keywords : *4-hydroxy benzaldehyde / phenothiazines / microwave irradiation / acetophenone / antibacterial activity.*

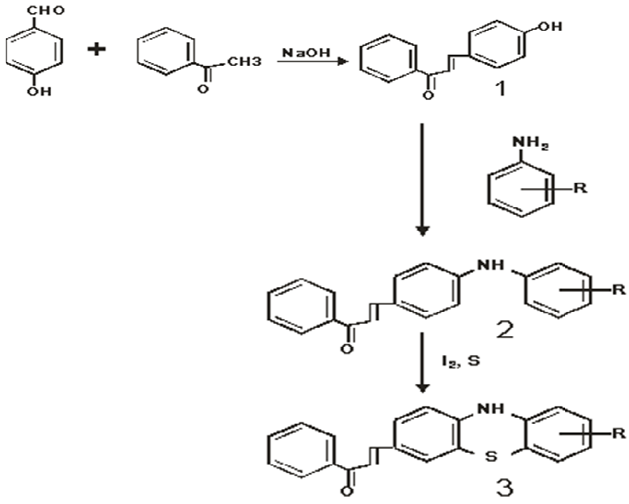
INTRODUCTION

The chemistry of chalcones has generated intensive scientific interest due to their biological properties such as antibacterial[1], antifungal[2], insecticidal[3], anaesthetic, antiinflammtory, analgesic, ulcerogenic[4-5] etc. Some substituted chalcones and their derivatives, including some of their heterocyclic analogues, have been reported to possess some interesting biological properties[6-9] which are detrimental to the growth of microbes tubercle bacilli, malarial parasites, acrus, Schistosoma, and intestinal worms, Some of the compounds are claimed to be toxic to animals and insect and are also reported to exhibit inhibitory action on several enzymes, fungi, and herbaceous plants. Phenothiazine heterocyclic ring system consisting of two benzene ring ortho fused to 1,4 thiazine ring and their analogs constituents an important class of bioactive heterocyclic reaction. They possess a wide spectrum of pharmalogical and biological activities[10-14] and their several derivatives are in clinical use. They are associated with biological activities like antibacterial, antiviral, anti-inflammatory, antifungal, antituberculosis, antibiotic, antileprous[15] psychotherapy[16] anabolic, analgesics agents, agricultural fungicide and in acutely ill HIV-infected

patients[16-18]. Microwave-induced Organic Reaction Enhancement (MORE) is used for carrying out chemical transformations. The microwave assisted organic reactions are more safe and an environmentally friendly with enhanced purity and yields of products. Shorter reaction time periods and higher yields render the microwave method superior to the classical method[19].

MATERIALS AND METHODS

Melting points were determine in oil bath using thermometer and were uncorrected. Purity of the compounds was checked on TLC using iodine vapor as visualizing agent. The IR spectra were run in KBr on a Perkins-Elmer infrared spectrophotometer. NMR spectra on Bucker AC- 300F (300Hz) NMR spectrometer using DMSO as a solvent using tetramethyl silence as internal standard.



R
3a - H
3b - 2OH
3c - 3OH
3d - 4OH
3e - $2NO_2$
3f - $3NO_2$
3g - $4NO_2$
3h - $N(CH_3)_2$
3i - Cl
3j - OCH_3

Synthesis of 3 form 2
By microwave irradiation method
A) Solid phase MWI-A solution of **2** (0.01mol), iodine and sulphur (0.01mol)in ethanol(2ml)was taken in a 100ml borosil flask and to this KOH(1g) and basic alumina (3g)was added. The reaction mixture was thoroughly mixed, dried in air and irradiated inside a microwave oven for 2-3 min. at power level (700W); the reaction mixture was cooled and extracted with ethanol (3x10ml).The resultant solid was recrystallized using aqueous ethanol.

B) Solution phase MWI- Equimolar quantities of **2** iodine and sulphur (0.01mol) in ethanol (30ml) were taken in a 100ml borosil flask fitted with a funnel as a loose top. The reaction mixture was irradiated in a microwave oven for 5-6 min. at 20% power level (300w) with short interruption of 20 sec. to avoid the excessive evaporation of the solvent. This protocol was repeated in overall heating time. On completion of the reaction (TLC) the reaction mixture was cooled and acidified with dil. HCl. The product **3**separated was filtered and washed with cold water, dried and recrystallized from ethanol.

General procedure
1-(4-phenyl)-3-(4'-hydroxyphenyl)-2-propen-1-one [1]: Acetophenone (0.01mol) and 4-hydroxy benzaldehyde (0.01mol) was dissolved in 100ml ethanol. To this solution, NaOH (40%, 10ml) was added drop wise with constant stirring at room temp. till a dark yellow mass was obtained. The reaction mixture was kept 7-8 hr and acidified with dil HCl. The soild obtained was washed with cold water it was filtered and dried. It was crystallized from ethanol. Yield 85%M.P153^{o}C.

2-(4-phenyl)-3-(4'-aminophenyl) aryl-2-propen-1-one [2]: When1-(4-phenyl)-3-(4-hydroxyphenyl)-2-propen-1-one**1** (0.05molewith different aromatic primary amine (0.05mole) in absolute ethanol (50ml) was heated under reflux in the presence of anhydrous. $Zncl_2$ (0.5g) for 6 hr. in a water bath. On cooling a solid mass separated out which was wash with from ethanol.

2-(propen-1-one) aryl-3-substituted phenothiazines [3] : A mixture of 1-(4-phenyl)-3-(4'-aminophenyl)-2-propen-1-one **2** .(0.01mole) , sulphur (0.1mole) and Iodine (0.5g) was rapidly heated at 120^{0}C in an oil bath for 2hr.The hot melt was rapidly poured in to a morter and crushed to a fine powder to give 3. It was washed with water dried and crystallized from ethanol.

2-(propen-1-one) aryl-3-substituted phenothiazines [3a] : M.F. $C_{21}H_{15}ONS$, Yield 62%, M.P.147^{0}C, IR; 1380(C-S),1495-1605(ArC=C), 3492 (NH-phenothiazine),1635(ArH), 740(C-S); NMR δH(ppm): 3.41(S,3H), 6.80(d,1H J=8Hz)6.83(d,1H J=8.5Hz), 6.96(t, 1H, J=7.6Hz) 7.14(dd, 1H, J=7.4Hz), 7.18(m,1H), 7.40(d,1H, J=15.6Hz), 7.42 (dd, 2H, J=7.8Hz), 7.50(t, 2H, J=7Hz) 7.58(t, 1H), 7.71(d, 1H, J=15.6), 8.00(dd, 2H J=7.8Hz).

2-(propen-1-one) aryl-3-substituted phenothiazines [3b] : M.F. $C_{21}H_{15}O_2NS$, Yield 79%, M.P.150^{0}C; IR(KBr); 3333 (-NH), 1630 (ArH), 1510-1630(ArC=C) , 655(C-S-C), NMR δH(ppm):3.38(s,3H); 6.76(m,2H); 6.98(m,1H), 7.04(dd,1H); 7.29(m,1H); 7.31(d,1H); 7.34(m,2H), 7.54(t,1H); 7.87(d,1H); 8.30(m,1H); 8.43(m,1H); 8.78(t,1H).

2-(propen-1-one) aryl-3-substituted phenothiazines [3c] : M.F $C_{21}H_{15}O_2NS$., Yield 80%, M.P.175^{0}C; IR(KBr); 3320 (-NHstr), 1630 (ArH), 1510-1630(ArC=C), 645(C-S-C) NMR δH(ppm):3.40(s,3H); 6.86(m,2H); 6.97(m,1H), 7.14(dd,1H); 7.19(m,1H); 7.39(d,1H); 7.40(m,2H), 7.72(t,1H); 7.78(d,1H); 8.34(m,1H); 8.42(m,1H); 8.82(t,1H).

2-(propen-1-one) aryl-3-substituted phenothiazines [3d] : M.F. $C_{21}H_{15}O_2NS$, Yield 81%, M.P.169^{0}C; IR(KBr); 3328 (-NHstr), 1610 (ArH), 1520-1630(ArC=C) , 645(C-S-C) NMR δH(ppm):3.40(s,3H); 6.84(m,2H); 6.70(m,1H), 7.15(dd,1H); 7.20(m,1H); 7.41(d,1H); 7.43(m,2H), 7.70(t,1H); 7.80(d,1H); 8.35(m,1H); 8.39(m,1H); 8.80(t,1H).

2-(propen-1-one) aryl-3-substituted phenothiazines [3e]: M.F. $C_{21}H_{14}O_3N_2S$, Yield 85%, M.P.213^{0}C; IR(KBr); 3570 (-NHstr), 1630 (ArH), 1530-1630(ArC=C) , 655(C-S-C). NMR δH(ppm):3.42(s,3H); 6.74(m,2H); 6.97(m,1H), 7.14(dd,1H); 7.21(m,1H); 7.37(d,1H); 7.40(m,2H), 7.72(t,1H); 7.78(d,1H); 8.34(m,1H); 8.42(m,1H); 8.83(t,1H).

2-(propen-1-one) aryl-3-substituted phenothiazines [3f] : M.F. . $C_{21}H_{14}O_3N_2S$, Yield 73%, M.P.180^{0}C; IR(KBr); , 3490 (-NHstr), 1630 (ArH), 1510-1630(ArC=C) , 655(C-S-C); NMR δH(ppm):3.40(s,3H); 6.76(m,2H); 6.95(m,1H), 7.16(dd,1H); 7.2 (m,1H); 7.4(d,1H); 7.44(m,2H), 7.72(t,1H); 7.78(d,1H); 8.34(m,1H); 8.42(m,1H); 8.85(t,1H).

2-(propen-1-one) aryl-3-substituted phenothiazines [3g] : M.F. . $C_{21}H_{14}O_3N_2S$, Yield 79%, M.P.185^{0}C; IR(KBr); 3490 (-NHstr), 1630 (ArH), 1510-1630(ArC=C) , 655(C-S-C); NMR δH(ppm):3.40(s,3H); 6.86(m,2H); 7.01(m,1H), 7.15(dd,1H); 7.19(m,1H); 7.39(d,1H); 7.40(m,2H), 7.72(t,1H); 7.78(d,1H); 8.34(m,1H); 8.41m,1H); 8.29(t,1H).

2-(propen-1-one) aryl-3-substituted phenothiazines [3h] : M.F. $C_{23}H_{20}ON_2S$, Yield 65%, M.P.180^{0}C; IR(KBr); 3490 (-NHstr), 1630 (ArH), 1510-1630(ArC=C) , 655(C-S-C); NMR δH(ppm):3.40(s,3H); 6.86(m,2H); 6.97(m,1H), 7.14(dd,1H); 7.19(m,1H); 7.39(d,1H); 7.40(m,2H), 7.72(t,1H); 7.78(d,1H); 8.24(m,1H); 8.65(m,1H); 8.2(t,1H).

2-(propen-1-one) aryl-3-substituted phenothiazines [3i] : M.F. $C_{21}H_{14}ONSCl$, Yield 77%, M.P.186^{0}C; IR(KBr); 3325 (-NHstr), 1635 (ArH), 1515-1620(ArC=C) , 656(C-S-C) NMR δH(ppm); 3.32(s,3H); 6.73(d,1H); 6.77(d,1H), 6.90(m,1H); 7.07(d,1H); 7.11(m,1H); 7.27(d,1H), 7.32(m,2H); 7.40(d,2H); 7.65(d,1H); 7.89(d,1H).

2-(propen-1-one) aryl-3-substituted phenothiazines [3j] : M.F. . $C_{22}H_{17}O_2NS$, Yield 73%, M.P.207C; IR(KBr); 3340 (-NHstr), 1628 (ArH), 1510-1630(ArC=C) , 658(C-S-C) NMR δH(ppm):3.40(s,3H); 3.89(s,3H); 6.80(d,1H); 6.83 (dd,1H), 6.94(m,1H); 6.99 (d, 2H); 7.19(dd,1H); 7.18 (m,1H); 7.42(dd,1H); 7.70(d,1H); 8.04(d,1H).

RESULTS AND DISCUSSION

The starting material 1-(4-phenyl)-3-(4'-hydroxyphenyl)-2-propen-1-one **1** was prepared by the reaction of acetophenone with 4-hydroxy benzaldehyde in presence of 40% NaOH which on treatment with substituted aniline to gives 1-(4-phenyl)-3-(4'-aminophenyl) aryl-2-propen-1-one **2** which undergoes cyclization with sulphur in presence of iodine catalyst gives 2-(propen-1-one) aryl-3-substituted phenothiazine **3**. The strunthctural assigment of synthesized compound is based on the spectral data. IR spectral band of all the compound indicates peak at 690-840cm^{-1} (substituted phenyl) and there exhibit a single sharp peak in the region 3410-3275 due to N-H stretching vibration there are number of peaks at 1020-1340, 1400-1500,3050 and 3300-3400 for C-N stretching, C=C starching, aromatic Ar-H stretching and N-H stretching respectively.pmr spectra indicates a singlet in the region δ

9.72-9.18ppm is due to N-H protons. Multiplate due to aromatic proton appeared in the region δ 8.40-6.32 ppm. The m/z molecular ion peak for 1, 2, 3 appeared at 224,298, 328 respectively. The reaction should be conducted under solvent free conditions with no side product formation and with utmost atom economy. In classical method the yield is lower as compared to microwave irradiation. Microwave irradiation facilitates the polarization of the molecule under irradiation causing rapid reaction.A comparative study in terms of yield and reaction period is shown in tableI.

Table-I-comparative study of compound 3a-j

Comp.	M.P. (^{0}C)	Reaction time Microwave(min) Solid phase	solvent phase	classical(hr)	Yield(%) Microwave Solid phase	solvent phase	classical
3a	147^{0}C	5	6	8	80	70	62
3b	150^{0}C	6	6	8	70	80	70
3c	175^{0}C	5.5	6.5	7	65	75	85
3d	169^{0}C	6	6	8	75	88	60
3e	213^{0}C	5	7	7	75	80	56
3f	189^{0}C	6	6	8	85	90	60
3g	185^{0}C	5	7	7	50	70	50
3h	180^{0}C	5.5	6	8	65	80	40
3i	186^{0}C	6	7	7	76	83	40
3j	207^{0}C	5	7	7	87	65	56

Table II- Antibacterial and Antifungal activities of compound 3a-j.

Antibacterial activities **Antifungal activities**

Compd.	**S.**aureus	B.substillis	E.coli	C.albicans	A. niger
3a	+ +	+ +	+	+ +	+ +
3b	+ +	+ +	+ + +	+ +	+ +
3c	+ + +	+ + +	+ + +	-	+ +
3d	+ +	+ +	+ +	+ +	+ +
3e	+	+ +	+	+ +	-
3f	+ + +	+ +	+ + +	+ +	+ +
3g	+ + +	+ +	+ + +	+ + +	+
3h	+ +	+ + +	+ +	+ + +	+ +
3i	+ + +	+ +	+ +	+ +	+ +
3j	+ +	+ +	+ +	+ +	+ +
SM	+ + +	+ + +	+ + + +		
GF				+ + + +	+ + +

SM (Streptomycin) and GF (Griesofulvin). The inhibition diameter in Mm: (-)<6, (+)7-9, (++)10-15, (+++)16-22, (++++)23-28.

Table III – characterization data of newly synthesized compound

Comp.	R	Mol. Formula	M.P. ^{0}C	yield (%)	**Elemental analysis** C	H	N	S
3a	-H	$C_{21}H_{15}ONS$	147	62	80 (80.1)	4.7 (4.5)	4.44 (4.5)	10.2 (10.5)
3b	2-OH	$C_{21}H_{15}O_2NS$	150	79	73.04 (73.05)	4.34 (4.5)	4.05 (4.0)	9.27 (9.5)
3c	3-OH	$C_{21}H_{15}O_2NS$	175	80	73.04 (73.05)	4.34 (4.5)	4.05 (4.0)	9.27 (9.5)
3d	4-OH	$C_{21}H_{15}O_2NS$	169	81	73.04 (73.05)	4.34 (4.5)	4.05 (4.0)	9.27 (9.5)
3e	2-NO_2	$C_{21}H_{14}O_3N_2S$	213	85	67.37 (67.27)	3.74 (3.5)	7.48 (7.43)	8.55 (8.5)
3f	3-NO_2	$C_{21}H_{14}O_3N_2S$	180	73	67.37 (67.27)	3.74 (3.5)	7.48 (7.43)	8.55 (8.5)
3g	4-NO_2	$C_{21}H_{14}O_3N_2S$	185	79	67.37 (67.27)	3.74 (3.5)	7.48 (7.43)	8.55 (8.5)
3h	-N(CH_3)	$C_{23}H_{20}ON_2S$	186	65	74.19 (74.20)	5.37 (5.5)	7.52 (7.49)	8.60 (8.55)
3i	-Cl	$C_{21}H_{14}ONSCl$	186	77	69.42 (69.40)	3.85 (3.80)	3.85 (3.82)	8.81 (8.85)
3j	-OCH_3	$C_{22}H_{17}O_2NS$	207	73	73.53 (73.52)	4.73 (4.70)	3.89 (3.83)	8.951 (8.9)

The compounds 3a-j were screened for their antibacterial activity against Bacillus subtilis, staphylococcus aureus and Escherichia coli., A. nigar by filter paper disc technique. Standard antibacterial Streptomycin and antifungal Griscofulvin . Results are presented in **table II.**

CONCLUSION

During our synthesis, we have used microwave methodology for the synthesis of 2-(propen-1-one) aryl-3-substituted phenothiazines. Microwave assisted organic synthesis have fascinated the chemist due to its usefulness with reduction of reaction time, enviremental friendly methodology etc. Compound 3b, 3d, 3f, 3j was effective against E.coli, S.aures, B.substillis, C. albicans, A. niger and compound 3a,3c,3e,3g, 3i effective against C.albicans, A. niger.

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