

One-pot Synthesis of Chalcone Derivatives By Using Anhydrous AlCl₃ as Condensing Agents

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ABSTRACT: Chalcones are α -unsaturated keto group containing compound. Chalcones are 1, 3-diphenyl-2-propene-1-one, consist of two aromatic rings linked by a three carbon α , β -unsaturated carbonyl system.

Heterocyclic compounds having nitrogen and sulphur in their skeleton are the most fascinated compound by scientists due to their diverse biological activities. Imidazoles have occupied a unique position in heterocyclic chemistry, and its derivatives have attracted considerable interests in recent years for their versatile properties in chemistry and pharmacology

Different methods are available for the preparation of chalcones²⁻⁴. The most convenient method is the Claisen-Schmidt condensation of aryl methyl ketone with aromatic aldehyde in presence of aqueous solution of sodium hydroxide⁵ at room temperature. Chalcones are used to synthesize several derivatives like cyanopyridines, pyrazolines isoxazoles and pyrimidines having different heterocyclic ring systems.⁶⁻⁹

The synthesized compounds were evaluated for antimicrobial and antifungal activity by disc diffusion method. The antifungal activity was evaluated against *A. niger*, *A. flavus* (fungal strains) using nystatin as the standard drugs. The antibacterial activity was evaluated *E. coli* and *S. aureus* using ciprofloxacin as the standard drugs. activity.

KEY WORDS: Chalcone, Claisen-Schmidt condensation, solvent-free synthesis, Antibacterial activity

INTRODUCTION

Diseases caused by pathogenic bacteria still attract significant attention from medicinal chemists and biologists because of growing antibacterial resistance.

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The synthesized compounds were evaluated for antimicrobial and antifungal activity by disc diffusion method. The antibacterial and antifungal activity was evaluated against *A. niger*, *A. flavus* (fungal strains), *E. coli* and *P. aeruginosa* (Gram negative bacteria), *S. aureus* and *S. pyogenes* (Gram positive bacteria) using Nystatin (for fungi) and ciprofloxacin (for bacteria) as the standard drugs.

The chalcones are associated with different biological activities like insecticidal⁹, anticancer¹⁰, anti-inflammatory¹¹, bactericidal¹², fungicidal¹³, antiviral¹⁴, antitumor¹⁵, antimalarial¹⁶ and antiulcer¹⁷. Literature shows that lieochalcone and oxygenated chalcone has strong antileishmanial activity^{18, 19}. It is reported that chalcones exhibited potent activity against human malarial parasite²⁰.

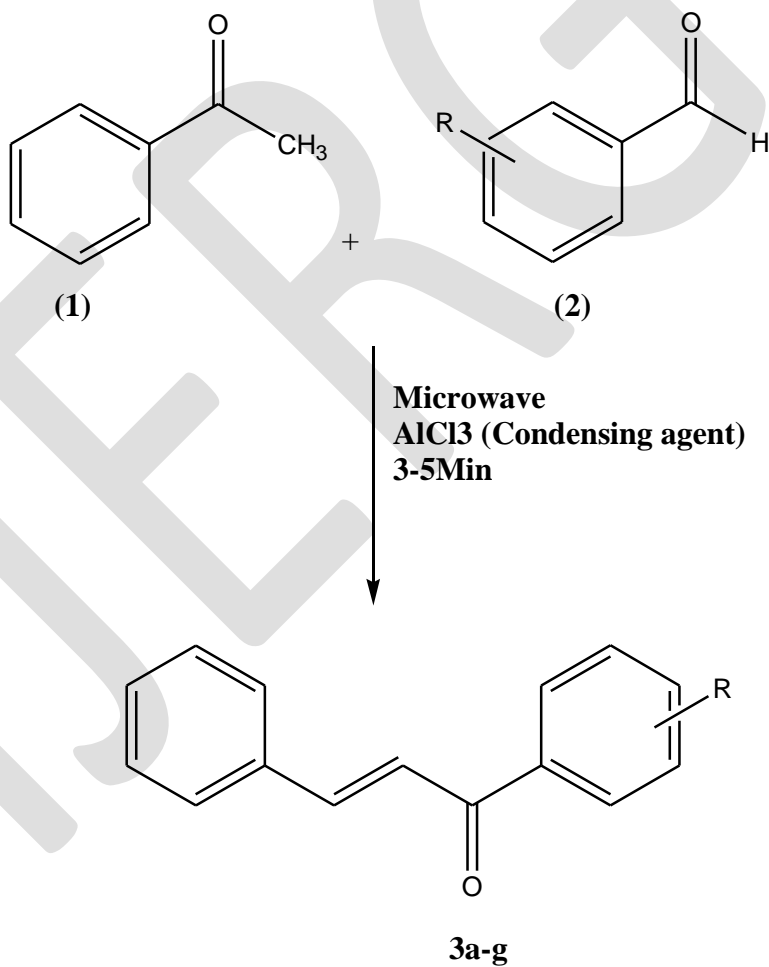
Chalcones are well known intermediates of various heterocyclic compounds. The compounds with the backbone of chalcones have been reported to possess various biological activities such as antimicrobial, anti-inflammatory, analgesic, anti ulcerative, antimalarial, anticancer, antiviral, Antioxidant, Anti tubercular, anti hyperglycemic, activities. The presence of a reactive keto-ethylenic group in chalcones is responsible for their antimicrobial activity.

Chalcones and their derivatives also used as artificial sweeteners^{21, 22}, scintillator²³, polymerization catalyst²⁴, fluorescent whitening agent²⁵.

EXPERIMENTAL SECTION

Melting points were determined by open glass capillary method and are uncorrected. All chemicals used were reagent grade and were used as received. A Laboratory Microwave Oven (Model BP 310/50) operating at 2450 MHz and power output of 600 W was used for all the experiments. The completion of reactions was monitored by TLC (Merk silica gel). IR spectra were recorded on a Shimadzu FTIR-420 spectrophotometer. ¹H NMR and ¹³C NMR spectra were recorded at 400°C on a Bruker AVANCE DPX (400 MHz) FT spectrometer in CDCl₃ using TMS as an internal reference (chemical shift in δ , ppm). Mass spectra were recorded on JEOL SX-303 (FAB) mass spectrophotometer at 70ev.

Scheme-I



GENERAL METHODS AND MATERIALS:

Thermal Method for synthesis of Chalcone (3a-i)

A mixture of substituted aromatic aldehyde (0.01 mol) and acetophenones (0.01 mol) was stirred (at specific time mention in table-2) along with absolute alcohol (40 ml) and then an aqueous solution of NaOH (15 ml) was added to complete the reaction. The mixture was kept overnight at room temperature and next day it was poured into crushed ice/ice chilled water and dil. HCl is used for the acidification. The Chalcone derivative precipitates out as solid. Progress of the reaction was monitored by TLC (Hexane: Ethyl Acetate, 6:1 v/v). The product was extracted with ethanol (3x50 mL). The extract was evaporated under reduced pressure to obtain the final product which was recrystallised from ethanol to get analytically pure compounds (3a-i)

Microwave irradiation for synthesis of Chalcone (3 a-i)

A mixture of substituted aromatic aldehyde (0.01 mol) and acetophenones (0.01 mol) along with condensing agent $AlCl_3$ were taken in 20 ml beaker and subjected to microwave irradiation at 200-300 W for 1 min. The reaction mixture was then thoroughly mixed outside the microwave oven and again irradiated for another few min in oven. This irradiation-mixing cycle was repeated for the total irradiation time **Table I**. The mixture was kept overnight at room temperature and next day it was poured into crushed ice/ice chilled water and dil. HCl is used for the acidification

After completion of the reaction as indicated by TLC (Hexane: Ethyl Acetate, 6:1 v/v) the product was extracted with ethanol (3x8 mL). The final product was recrystallised from ethanol to obtain analytically pure compounds (3a-i).

Melting point and Yield of Compound 3_{a-g}

Comp ound	R	Time		Yield (%)		M. P. (°C)
		MWI (min)	Stirring at temperature 50°C(hour)	MWI	Thermal	
3a	H	3	8	78	35	58
3b	4-Cl	2	7	85	32	160
3c	4-HO	2	7	88	33	150
3d	4-MeO	2	8	85	34	105
3e	2-NO ₂	3	7	89	33	147
3f	3-MeO, 4-HO	3	7	85	35	145
3g	2-NH ₂	2	7	85	36	90

Table 2: Physical and spectral data of compounds 3_{a-g}

Compd.	Mol.Formulla	1 H-NMR (Cde _l ₃ , Δ, Ppm)	Elemental Analysis	MS (EI, M/Z (M ⁺))

3a	C ₁₃ H ₁₀ O	7.14-7.30 (m,5H,ArH),7.56-7.90 (s,2H,-CH=CH-),7.45- 7.80(m,5H,ArH)	C:86.51,H:5.81,O:7.68	208
3b	C ₁₅ H ₁₁ OCl	7.14-7.30 (m,5H,ArH),7.56-7.90 (s,2H,-CH=CH-),7.45- 7.75(m,5H,ArH)	C:74.23,H:4.57,Cl:14.61,O : 6.59	242
3c	C ₁₅ H ₁₂ O ₂	7.14-7.30 (m,5H,ArH),7.56-7.90 (s,2H,-CH=CH-) ,5.00(s,1H,OH),6.92- 7.64(m,4H,ArH)	C:80.34,H:5.39, O:14.27	224
3d	C ₁₆ H ₁₄ O	7.14-7.30 (m,5H,ArH),7.56-7.90 (s,2H,-CH=CH-) ,2.53(s,1H,CH ₃),6.92- 7.55(m,4H,ArH)	C:86.45, H:6.35,O:7.20	222
3e	C ₁₅ H ₁₁ NO ₂	7.14-7.30 (m,5H,ArH),7.56-7.90 (s,2H,-CH=CH-) ,2.53(s,1H,CH ₃),8.07- 8.38(m,4H,ArH)	C:71.14,H:4.38,N:5.53, O:18.95	253
3f	C ₁₆ H ₁₄ O ₃	7.14-7.30 (m,5H,ArH),7.56-7.90 (s,2H,-CH=CH-) ,3.73(s,3H,CH ₃),5.00(s,1H ,OH),6.81-7.20(m,4H,ArH)	C:75.57,H:5.55,O:18.88	254
3g	C ₁₅ H ₁₃ NO ₃	7.14-7.30 (m,5H,ArH),7.56-7.90 (s,2H,-CH=CH-) ,3.73(s,2H,NH ₂),6.65-7.56 (m,4H,ArH)	C:80.69,H:5.87,N:6.27; O:7.17	223

ANTIMICROBIAL ACTIVITY

The synthesized)compounds **3a-g** was evaluated for antibacterial and antifungal activity by disc diffusion method. The presence of α , β -unsaturated carbonyl system of chalcone makes it biologically active. The antifungal activity was evaluated against *A. niger*, *A. flavus* (fungal strains) using nystatin as the standard drugs. The antibacterial activity was evaluated *E. coli* and *S.aureus* using ciprofloxacin as the standard drugs. The results of antibacterial and antifungal activities studies are given in **Table-3**.

Table 3: Antibacterial and Antifungal Activities of compounds 3_{a-g}

Compd.	Antibacterial		Antifungal	
	<i>S. aureus</i>	<i>E. coli</i>	<i>A. niger</i>	<i>A. Flavus</i>
3a	8	9	6	7
3b	14	15	12	13
3c	13	13	11	12
3d	12	12	10	10
3e	14	13	11	12

3f	12	13	11	13
3g	13	14	12	12
Ciprofloxacin	16	16	-	-
Nystatin	-	-	13	14

The results show that majority of the synthesized compounds showed varying degrees of activity against bacteria and fungi. The 3b and 3g showed antibacterial and antifungal excellent activity against *S. aureus* and *E. coli*. Whereas the compounds 3c, 3d, 3e, 3f have shown good to moderate activity against *S. aureus* and *E. coli* at concentration 500 µg/ml.

RESULTS & DISCUSSION

Claisen-Schmidt condensation of acetophenone with aromatic aldehyde by using $AlCl_3$ as condensing agent under solvent-free gave regioselective Chalcone derivatives **3a-g**. The Structure of **3a-g** was supported by 1H NMR and elemental spectral analysis. The reactions were also carried out using a water bath at the same temperature. It was found that MW method has improved the yields significantly. MW enhancement of yields and reduction in reaction time can be rationalized on the basis of the formation of dipolar activated complex and greater stabilization of the more dipolar activated complex by dipole-dipole interaction with electric field of the microwaves as compared to the less polar adduct which may reduce the activation energy resulting in the rate enhancement.

The synthesized compounds **3a-g** was evaluated for antibacterial and antifungal activity by disc diffusion method. The results show that majority of the synthesized compounds showed varying degrees of activity against bacteria and fungi.

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REFERENCES:

1. M. A. El.Hashah; M. El-Kady; M. A. Saiyed and A. A. Elawwy, Egypt. J. Chem., **27**, 715 (1985).
2. L. S. Crawley and W. J. Fanshawe, J. Heterocyclic chem., **14**, 531 (1977).
3. E. C. Taylor and R. W. Morrison, J. Org. Chem., **32**, 2379 (1967).
4. P. S. Utale, P. B. Raghuvanshi and A. G. Doshi, Asian J. Chem., **10**, 597 (1998).
5. H. Rupe and D. Wasserzug, J. Chem. Ber., **34**, 3527 (1901).
6. S. A. Hermes, Chem. Ber., **70**, 96422h (1969).
7. D. S. Breslow and C. R. Houser, Chem. Ber., **62**, 2385 (1940).
8. K. Kazauki, K. Hitayama, S. Yokomori and T. Soki, Chem. Abstr., **85**, 591(1976).
9. M. Larsen, H. Kromann, A. Kharazmi and S. F. Nielsen, Bioorg. Med. Chem. Lett., **15**, 4858 (2005)
10. G. Zongru, H. Rui, F. Z. Shenquang and G. Shuminshu, Chem. Abstr., **125**, 10376r (1996)
11. H. Serre, J. Rey and J. P. Tarayre, Chem. Abstr., **91**, 9494a (1979)
12. S. F. Nielsen, T. Boson, M. Larsen and H. Kromann, Bioorg. Med. Chem. Lett., **12**, 3047 (2004)
13. A. K. Padersen and G. A. Fitz, J. Pharm. Sci., **74**, 188 (1985)
14. D. Binder, C. R. Noe, W. Holzer and B. Rosenwirth, Arch. Pharm., **318**, 48 (1985)
15. Y. Satomi, Ind. J. Cancer, **120**, 208071 (1994)
16. A. Vall, B. Vall, D. Cartier and J. Schrevel, Euro. J. Med. Chem. (in press) 2005.
17. Tashio pharmaceutical Ltd., Chem. Abstr., **101**, 54722j (1984)
18. C. M. Christesen, S. B. Blom and L. Fich, Antimicrobial agents and chemotherapy, **37**, 2550 (1993)
19. M. Chen, S. B. Christensen and T. G. Theander, Antimicrobial agents and chemotherapy, **38**, 139 (1994)
20. C. M. Christensen, S. B. Zhai and M. H. Theander, J. Of Infectious Diseases, **176**, 1327 (1997).
21. R. M. Horowitz and B. Gentili, U. S. Patent, **3**, 890, 298 (1975), Chem. Abstr., **83**, 147706g, (1975)
22. G. P. Rizzi and J. S. Neely, German Patent, **2**, 148, 332 (1972); Chem. Abstr., **11**, 86777h (1972)

23. M. Delcarmen, G. Barrio, J. R. Barrio, G. Walker, A. Noveli and N. J. Leonard, J. Am. Chem. Soc, **95**, 4891 (1973)
24. Mitsubishi Petrochemical Co. Ltd., British Patent **1**, 128, 090 (1968); Chem. Abstr., **69**, 97342y (1968)
25. G. Hayakawa and T. Inoue, Japanese Patent 7, **107**, 386 (1971); Chem. Abstr., **74**, 14332y (1971)

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