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Research Article

"SYNTHESIS OF SUBSTITUTED CHALCONES UNDER SOLVENT–FREE MICROWAVE IRRADIATION CONDITIONS AND THEIR ANTIMICROBIAL EVALUATION"

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ABSTRACT

The microwave assisted synthesis of nine chalcones (iii a-i) was carried out by irradiating the aldehyde (3-methoxy, 4-methoxy, 3,4,5-trimethoxy substituted) and acetophenone (4-amino, 4-nitro substituted) in the presence of zinc chloride. Minor quantities of Ketol and Michael addition products were easily removed by recrystallization. An efficient solvent free synthesis of these nine chalcones (iii a-i) involving aldol condensation was also carried out by grinding the reactants in presence of solid sodium hydroxide with a mortar and pestle. The results of both the methods were found similar when correlated. In general, the chalcones were obtained in high yield and purity. The compounds obtained were identified by elemental analysis, IR, ^{1}H NMR, ^{13}CNMR and mass spectral data. These compounds were screened for their antimicrobial activity.

Keywords: Microwave irradiation, Solvent free synthesis, Chalcone, Aldol condensation, Antimicrobial activity.

INTRODUCTION

1,3-Diphenyl propenones (chalcones) are well known to exhibit a broad spectrum of biological activities[1]. These are main precursors in the biosynthesis of flavonoids[2] that are abundant in edible plants. They have been reported to possess various pharmacological activities like anticancer[3,4], antimalarial[5], antiplasmodial[6], anti-inflammatory[7], antitubercular[8], cytotoxic[9], antidepresent[10], antibacterial[11], antiHIV[12], antifouling[13], trypanocidal[14], leishmanicidal[15], gastroprotective[16], modulation of nitric oxide production[17] and so on. Additionally, some of chalcone derivatives have been found to inhibit several important enzymes in cellular systems, such as xanthine oxidase[18] and protein tyrosine kinase[19]. These compounds are valuable synthons for the preparation of five and six membered ring systems[20] as well as intermediate in the synthesis of many pharmaceuticals[21]. Because of their varied pharmacological activity and synthetic utility, much attention has been paid to develop newer strategies for the synthesis of such compounds.

The Claisen-Schmidt condensation of an appropriate acetophenone with benzaldehyde in presence of aqueous bases like KOH, NaOH[22], $Ba(OH)_2$[23] etc., is the most popular way to synthesize chalcones by far. Other base catalysts such as magnesium t-butoxide[24], potassium carbonate[25], alumina[26], MgO[27], calcinated hydrotalcites[28,29], natural phosphate/$NaNO_3$[30,31], KF/natural phosphate[32] and piperidine[33] have also been used for their synthesis. However all these methods have the common disadvantage of employing drastic reaction conditions and also producing several side products.

The exploitation of microwaves (MW) for assisting different organic solvents has blossomed into an important tool in the synthetic organic chemistry with large horizon of applications. Due to the timeless ease of workability and ecofriendliness, MW provides an alternative to environmentally unacceptable procedures, which may suffer from the drawbacks of lower yields and harsh environmentally detrimental reaction conditions. The condensation of appropriate acetophenone and substituted benzaldehyde in the presence of anhydrous $ZnCl_2$ via microwave assisted path[34] yielded the corresponding 1,3-diaryl chalcones[35,36]. In summary, this work demonstrates a rapid, efficient, economical and environmentally benign protocol for the synthesis of chalcones under microwave heating and the results obtained confirm the superiority of microwave irradiation method over the classical methods.

SCHEME-1

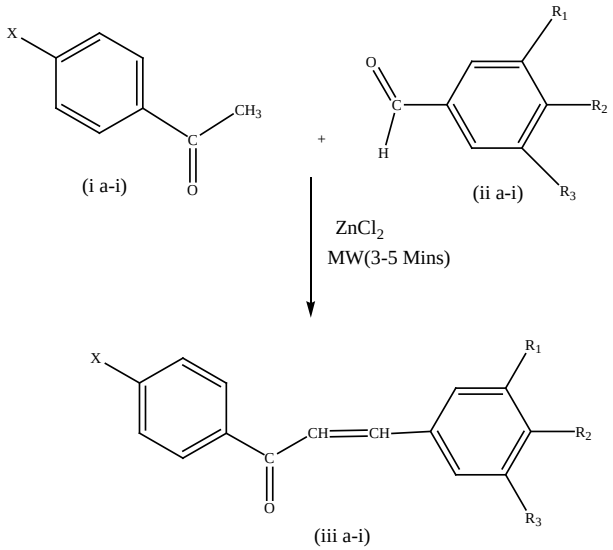

Fig. I: Synthesis of chalcones under microwave irradiation conditions

Table 1: Synthesis of Chalcones under microwave conditions

Compd.	X	R_1	R_2	R_3	Reaction Time(min.)
iii a	H	H	OCH_3	H	4
iii b	H	OCH_3	OCH_3	OCH_3	3
iii c	NO_2	H	OCH_3	H	4
iii d	H	OCH_3	H	H	4
iii e	NH_2	OCH_3	OCH_3	OCH_3	5
iii f	NH_2	H	OCH_3	H	5
iii g	NH_2	OCH_3	OCH_3	H	5
iii h	NO_2	OCH_3	OCH_3	OCH_3	4
iii i	H	OCH_3	OCH_3	H	4

MATERIALS AND METHOD

All commercially available chemicals and reagents were purchased from Aldrich and used without further purification. Melting points were determined in open capillaries and were uncorrected. The IR spectra were recorded in KBr disc on a Nicolet Megna-FTIR 550 spectrometer, ^1H and ^{13}C NMR on model DRX 300 at 300.13 and 75.48 MHz spectrometer in $CDCl_3$ / DMSO-d_6 using TMS as an internal standard. Mass spectra were recorded on a LC-MS-2010 data report SHIMADZU Spectrometer. Microwave reactions were carried out using LG555F multipower microwave oven operating at 2450 MHz frequency. Thin layer chromatography (TLC) was performed on silica coated aluminum plates (Merck) and spots were visualized by iodine vapors or by irradiation with ultraviolet lights (254 nm).

General procedure for the synthesis of chalcones (iii a-i)

(A) Solvent free synthesis (S.F.S.)

A mortar was charged with the acetophenone derivative (i a-i) (1mmol), aldehyde derivative (ii a-i) (1mmol), sodium hydroxide (0.04 g, 1mmol) and silica gel (0.1 g). The reaction mixture was ground with a pestle in the mortar. When TLC showed no remaining aldehyde or ketone, the reaction mixture was poured into a mixture of dichloromethane (20ml) and 5% HCl (10ml). The ethereal layer was washed with saturated $NaHCO_3$, dried ($MgSO_4$), and evaporated to give the pure product (iii a-i). Purity of compounds was checked by TLC using $CHCl_3$ as mobile phase.

(B) Microwave synthesis (m.s.)

A mixture of acetophenone derivative (i a-i) (0.01 mol), substituted aldehyde (ii a-i) (0.01 mol) and $ZnCl_2$ (0.001 mol) was taken in ACE tube, flushed with argon and tightly capped. The mixture was subjected to microwave heating for 3-5 min. in a domestic oven and allowed to reach the room temperature. The reaction mixture was treated with aq. ethanol (20 ml) and the separated solid was filtered, washed with *n*-hexane and dried. The solid (iii a-i) was recrystallized by benzene-hexane (figure-I).

SPECTRAL DATA

3-(4-Methoxyphenyl)-1-phenyl propenone (iii a)

Pale yellow needles, yield 92%, Melting point: (s.f.s.) 72-74^{0}C, (m.s.) 71-72^{0}C (benzene-hexane); IR (KBr): 1645cm^{-1}(C=O), 3040cm^{-1}(Ar-H), 1585cm^{-1}(C=C), 1175-1240cm^{-1}(asym. C-O-C), 1015-1055cm^{-1}(sym. C-O-C); ^{1}HNMR (300MHz, $CDCl_3$, δ, ppm): 6.92-8.04(m,9H, Ar-H),7.83(d,1H,αCH), 8.03(d,1H,βCH), 3.80(s,3H,OCH_3); ^{13}CNMR (75MHz, $CDCl_3$, δ, ppm): 186.0(C=O), 143.8,122.3(C=C), 56.4(-OCH_3); Found,%: C 80.62; H 5.93. $C_{16}H_{14}O_2$. Calculated, %: C 80.65; H 5.92. LCMS: 239(M+H$^+$).

1-Phenyl-3-(3, 4, 5-trimethoxyphenyl)-propenone (iii b)

Dark yellow solid, yield 86%, Melting point: (s.f.s.) 60-63^{0}C, (m.s.) 62-64^{0}C (benzene-hexane); IR (KBr): 1640cm^{-1}(C=O), 3035cm^{-1}(Ar-H), 1575cm^{-1}(C=C), 1170-1245cm^{-1}(asym. C-O-C), 1015-1050cm^{-1}(sym.C-O-C); ^{1}HNMR (300MHz, $CDCl_3$, δ, ppm): 6.50-8.03(m,7H,Ar-H), 7.81(d,1H,αCH), 8.02(d,1H,βCH), 3.86(s,9H,OCH_3) ; ^{13}CNMR (75MHz, $CDCl_3$, δ, ppm): 186.4(C=O), 144.1, 123.6(C=C), 56.4, 56.9, 56.5(-OCH_3); Found,%: C 72.48; H 6.03. $C_{18}H_{18}O_4$. Calculated, % C 72.47; H 6.08. LCMS: 299(M+H$^+$).

3-(4-Methoxyphenyl)-1-(4-nitrophenyl)-propenone (iii c)

Shiny yellow needles, yield 82%, Melting point: (s.f.s.) 162-163^{0}C,(m.s.)160-162^{0}C (benzene-hexane); IR (KBr): 1650cm^{-1}(C=O), 3055cm^{-1}(Ar-H), 1590cm^{-1}(C=C),1185-1255 cm^{-1}(asym. C-O-C),1025-1055cm^{-1}(sym. C-O-C); ^{1}HNMR (300MHz, $CDCl_3$, δ, ppm): 6.61-8.37(m,8H,Ar-H), 7.76(d,1H,αCH), 8.03(d,1H,βCH), 3.70(s,3H,OCH_3); ^{13}CNMR (75MHz, $CDCl_3$, δ, ppm): 186.3(C=O),143.9,122.1(C=C), 56.0(-OCH_3), 152.5(C-N); Found,% :C 67.85; H 4.62; N 4.96. $C_{16}H_{13}O_4N$. Calculated, % C 67.84; H 4.63; N 4.94. LCMS: 284(M+H$^+$).

3-(3-Methoxyphenyl)-1-phenyl propenone(iii d)

Pale yellow crystals, yield 88%, Melting point: (s.f.s.) 46-47^{0}C, (m.s.) 45-47^{0}C (benzene-hexane); IR (KBr): 1645cm^{-1}(C=O), 3035cm^{-1}(Ar-H), 1580cm^{-1}(C=C), 1170-1240 cm^{-1}(asym. C-O-C),1020-1060cm^{-1}(sym.C-O-C);^{1}HNMR(300MHz, $CDCl_3$, δ, ppm): 6.68-8.01(m,9H,Ar-H),7.83(d,1H,αCH), 8.03(d,1H,βCH), 3.78(s,3H,OCH_3); ^{13}CNMR (75MHz, $CDCl_3$, δ, ppm): 186.2(C=O),143.7,122.3(C=C),56.3(-OCH_3); Found,%: C 80.62; H 5.93. $C_{16}H_{14}O_2$. Calculated,%. C 80.65;H 5.92. LCMS: 239(M+H$^+$).

1-(4-Aminophenyl)-3-(3, 4, 5-trimethoxyphenyl)-propenone (iii e)

Dark yellow solid, yield 72%, Melting point: (s.f.s.) 128-129^{0}C, (m.s.) 126-129^{0}C (benzene-hexane); IR (KBr): 1655cm^{-1}(C=O), 3050cm^{-1}(Ar-H), 1585cm^{-1}(C=C), 1180-1250 cm^{-1}(asym. C-O-C), 1030-1045cm^{-1}(sym.C-O-C); ^{1}HNMR (300MHz, $CDCl_3$, δ, ppm): 6.62-7.95(m,6H,Ar-H), 7.74(d,1H,αCH), 8.01(d,1H,βCH), 3.81(s,9H,OCH_3); ^{13}CNMR (75MHz, $CDCl_3$, δ, ppm): 186.8(C=O), 144.2, 123.1(C=C), 56.7, 57.4, 56.9(-OCH_3),154.5(C-N); Found,% C 68.97; H 6.08; N 4.45. $C_{18}H_{19}O_4N$. Calculated, %: C 68.99; H 6.11; N 4.47. LCMS: 314(M+H$^+$).

1-(4-Aminophenyl)-3-(4-methoxyphenyl)-propenone (iii f)

Yellow amorphous solid, yield 73%, Melting point: (s.f.s.) 89-90^{0}C, (m.s.) 85-87^{0}C (benzene-hexane); IR (KBr): 1655cm^{-1}(C=O), 3042cm^{-1}(Ar-H), 1585cm^{-1}(C=C), 1180-1257 cm^{-1}(asym. C-O-C),1030-1060cm^{-1}(sym. C-O-C); ^{1}HNMR (300MHz, $CDCl_3$, δ, ppm): 6.64-8.05(m,8H,Ar-H), 7.79(d,1H,αCH), 8.04(d,1H,βCH), 3.68(s,3H,OCH_3); ^{13}CNMR (75MHz, $CDCl_3$, δ, ppm): 186.1(C=O), 143.8, 122.5(C=C), 55.8, 56.1(-OCH_3),153.2(C-N); Found,% C 75.86; H 5.98; N 5.51. $C_{16}H_{15}O_2N$. Calculated, %: C 75.87; H 5.97; N 5.53. LCMS: 254(M+H$^+$).

1-(4-Aminophenyl)-3-(3,4-dimethoxyphenyl)-propenone(iii g)

Dark yellow crystals, yield 79%, Melting point: (s.f.s.) 120-122^{0}C, (m.s.) 119-121^{0}C (benzene-hexane); IR (KBr): 1655cm^{-1}(C=O), 3045cm^{-1}(Ar-H), 1585cm^{-1}(C=C), 1180-1255cm^{-1}(asym. C-O-C), 1030-1065cm^{-1}(sym. C-O-C); ^{1}HNMR (300MHz, $CDCl_3$, δ, ppm): 6.64-8.02(m,7H,Ar-H), 7.77(d,1H,αCH), 8.02(d,1H,βCH), 3.72(s,6H,OCH_3); ^{13}CNMR (75MHz, $CDCl_3$,δ, ppm): 186.3(C=O), 144.1, 122.9(C=C), 56.2, 56.4(-OCH_3), 153.5(C-N); Found,% C 72.07; H 6.06; N 4.91. $C_{17}H_{17}O_3N$. Calculated, % C 72.08; H 6.05; N 4.94. LCMS: 284(M+H$^+$).

3-(3, 4, 5-trimethoxyphenyl)-1-(4-nitrophenyl)-propenone(iii h)

Yellow crystalline solid, yield 77%, Melting point: (s.f.s.) 101-102^{0}C, (m.s.) 101-104^{0}C (benzene-hexane); IR (KBr): 1640cm^{-1}(C=O), 3025cm^{-1}(Ar-H), 1575cm^{-1}(C=C), 1170-1230 cm^{-1}(asym.C-O-C),1010-1035cm^{-1}(symC-O-C);^{1}HNMR (300MHz, $CDCl_3$, δ, ppm):

6.22-8.37(m,6H,ArH), 7.84(d,1H,αCH), 8.01(d,1H,βCH), 3.93(s,9H,OCH_3); ^{13}CNMR (75MHz, $CDCl_3$, δ, ppm): 186.6(C=O), 144.9, 123.2(C=C), 56.3, 56.6, 56.3 (-OCH_3), 154.6(C-N); Found,% C 62.96; H 5.03; N 4.10. $C_{18}H_{17}O_6N$. Calculated, %: C 62.97; H 4.99; N 4.08. LCMS: 330($M+H^+$).

1-Phenyl-3-(3, 4-dimethoxyphenyl)-propenone(iii i)

Dark yellow crystals, yield 83%, Melting point: (s.f.s.) 102-106^{0}C, (m.s.)104-108^{0}C (benzene-hexane); IR(KBr): 1640cm^{-1}(C=O), 3025cm^{-1}(Ar-H), 1572cm^{-1}(C=C), 1170-1230 cm^{-1}(asym. C-O-C), 1010-1035cm^{-1}(sym. C-O-C); ^{1}HNMR (300MHz, $CDCl_3$, δ, ppm) : 6.48-8.01(m,8H,ArH), 7.80(d,1H,αCH), 8.01(d,1H,βCH), 3.83 (s,9H,OCH_3); ^{13}CNMR (75MHz, $CDCl_3$, δ, ppm): 186.5(C=O), 143.6, 123.2(C=C), 56.3, 56.6, 56.3(-OCH_3): Found,% C 76.08; H 6.05. $C_{17}H_{16}O_3$.Calculated, %: C 76.10; H 6.01. LCMS: 269($M+H^+$).

SCREENING FOR ANTIMICROBIAL ACTIVITY

All the synthesized heterocyclic compounds (iii a-i) were screened for their antibacterial activity against Zymomonal mobilis (gram negative) MTCC 88 and Staphylococcus aureus (gram positive) MTCC 3160 bacterial strains and antifungal activity against Fusarium culmorum MTCC 349 and Phanerochaete chrysosprium MTCC 787 fungal strains.

The agar well-diffusion method[37] was applied for the determination of inhibition zone and minimum inhibitory concentration (MIC). The medium was sterilized by autoclaving at 120° C (15 lb/in^2). Briefly, 100µL of broth culture containing test strain was added to 30 mL of nutrient agar (NA) medium (for antibacterial activity) and to 25 mL of potato dextrose agar (PDA) medium (for antifungal activity) at 37^{o}C. Mixed well and then poured aseptically into a 15 cm sterile metallic petri plate. The medium was allowed to solidify, and 8 mm wells were dug with a sterile metallic borer. Then, a DMSO solution of the test sample (1mL) at 1 mg/mL was added to the respective wells. DMSO served as a negative control.

The standard antimicrobial drugs (1mg/mL) Ampicillin (for bacterial assay) and (1mg/mL) Fluconazole (for fungal assay) were used as positive control. Triplicate plates of each microorganism strain were prepared and were incubated aerobically at 37±2°C for 24 h for antibacterial and 28 ± 2°C for 48 h for antifungal activity respectively.

The antimicrobial activity[38] was determined by measuring the diameter of zone showing complete inhibition (mm), thereby the zones were precisely measured with the aid of a Vernier Caliper (precision 0.1 mm). The growth inhibition was calculated with reference to the positive control.

Table 2: Antimicrobial Activity of Titled Compounds

Sample (iii a-i)	Minimum inhibitory concentration (MIC) values			
	Zymomonal mobilis	***Staphylococcus aureus***	***Fusarium culmorum***	***Phanerochaete chrysosprium***
iii a	9.6	12.5	16.6	34.6
iii b	31.2	9.6	12.5	16.6
iii c	18.7	16.6	18.7	12.5
iii d	12.5	33.7	28.1	32.5
iii e	12.5	8.7	12.5	9.6
iii f	16.6	9.6	28.5	8.7
iii g	18.7	7.7	9.6	16.6
iii h	16.6	30.2	29.3	9.6
iii i	9.6	8.7	8.7	12.5
Standard	7.2	5.1	8.0	8.3

RESULTS AND DISCUSSION

The structures of synthesized compounds (iii a-i) were confirmed on the basis of elemental and spectral analysis. Selected diagnostic bands of the IR spectra of (iii a-i) showed useful information about the structure of the title compounds. Further evidence for the formation of chalcones was obtained by recording the mass spectra which showed characteristic molecular ion peaks that are in conformity with the molecular formula of characteristic chalcone. The results reveal that chalcones were significantly effective against both Gram-positive and Gram-negative organism as well as against fungal strains also.

CONCLUSION

Due to stringent and growing environmental regulations, the chemical industry needs the development of more eco-compatible synthetic methodologies. The use of microwaves under solvent free conditions represents a potentially valuable and clean route to a range of organic products. Microwave assisted synthetic reactions are gaining importance in recent years because of its endorsement under Green chemistry protocol.

In conclusion, we have approached to an easy and convenient synthetic method for the preparation of substituted chalcones using microwave irradiations. The mild reaction conditions, zero side products, clean reaction profiles and cost efficiency render this approach as a useful alternative to the existing methods. Further studies on the application of this method for the synthesis of highly functionalized biologically active chalcones are underway.

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