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MICROWAVE ASSISTED SYNTHESIS AND ANTIBACTERIAL ACTIVIES OF SOME (*E*)-1-PHENYL-3-(2-THIOMORPHOLINOQUINOLIN-3-YL) PROP-2-EN-1-ONE USING BASIC CATALYST

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ABSTRACT

Synthesis of eight substituted chalcones using basic heterogeneous catalyst anhydrous K_2CO_3 under MWI was carried out to improve Claisen–Schmidt condensation reaction. A comparative aspect of different compounds in respect of catalyst, time taken and per cent of yield has been discussed. The advantages of this process is to design and develop new synthetic routes to various bioactive chalcone, which is environmentally desirable and economically viable. The structures of all the compounds have been established by spectral analysis such as IR, ^{1}H-NMR, ^{13}C-NMR and mass spectrometry. The synthesized compounds were also used for antimicrobial screening.

Key words: Quinoline, Thiomorpholine, Chalcone, Anhydrous K_2CO_3 catalyst, Microwave irradiation, Antibacterial activity.

INTRODUCTION

Quinoline derivatives exhibit extensively biological and pharmacological activities[1]. Plant sources Quinolines derivatives have shown to exhibit a variety of biological properties including antibacterial[2], antifungal[3], antiviral[4], anti-protozoal[5] and anti-platelet aggregation[6] activities. Also these compounds are found to be key intermediates in the synthesis of several furoquinoline and pyranoquinoline type heterocycles[7-9]. Thiomorpholine analogs are associated with a variety of pharmacological activities including antimycobacterial[10], antibacterial[11], antimalarial[12], and analgesic[13].

The chalcones are *α*, *β*-unsaturated ketones containing the reactive ketoethylenic group COCH=CH-. Presence of *α*, *β*-unsaturated carbonyl system in chalcone makes it

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biologically active. Chalcones have been used as intermediate for the preparations of many organic compounds having bioactivity. Literature review reveals that chalcone derivatives exhibit diverse pharmacological activities such as anti-AIDS[14], anti-inflammatory[15], anticancer[16], antitubercular[17], antibacterial[18], antioxidant[19], antimalarial[20] and antileishmanial[21] activity. They are commonly synthesized via the Claisen-Schmidt condensation between acetophenone and benzaldehyde. This reaction is catalyzed by acids and bases under homogeneous conditions. The reaction gives low yield, takes longer reaction time and presents several hurdles, such as catalyst recovery and waste disposal problems. In this respect, basic catalyst is considered as an eco-friendly alternative. The utilization of heterogeneous catalysts for the production of chalcones was reported in the literature[22-25]. Utilization of greener process *i.e*. non-conventional energy source like microwave[26] has become a very popular and useful technique in synthetic organic chemistry and has gained wide popularity due to many practical advantages associated with enhanced reaction rates, high yields, improved selectivity and environment friendly reaction conditions. Further studies on the efficient synthesis of chalcones are of current interest because of their wide range of applications. Keeping in view the biological importance of chalcones as antileishmanial agents[27] and our ongoing endeavors in the development of environmentally benign protocols related to chalcones, we now report facile non-conventional heterogeneous approach for the synthesis of substituted chalcones, substituted acetophenones and aromatic aldehydes using basic solid supports anhydrous K_2CO_3 under microwave irradiation. For comparison, the results under conventional method are also presented.

EXPERIMENTAL

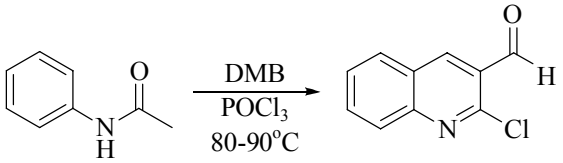
Melting points (mp) were determined using Boetieus micro heating table and are uncorrected. IR (KBr, cm^{-1}) spectra were obtained on Perkin- Elmer FT-IR spectrum BX. ^{1}H-NMR spectra were recorded on Bruker AMX-400 (400 MHz) spectrometer using TMS as an internal reference (Chemical shifts in δ, ppm). Mass spectra were recorded on Quatro Lc micromas (Waters Manchester.UK). (70 eV) mass spectrometer. For microwave irradiation a L.G. (M-2349E, 2450 MHz) domestic microwave oven was used. We performed disc diffusion method to identify the antimicrobial activity on gram positive bacteria *viz. staphylococcus aureus* and gram negative bacteria *viz. Escherichia coli* for which disc Whatmann filter paper discs were used.

Procedure

Step-1: Synthesis of 2-chloro-3-formyl quinoline (2)

The starting material compound 2-chloro-3-formyl quinoline **(2)** was synthesized by using the Vilsmeier-Haack reagent. Condensation of (**1)** with dimethyl formamide in $POCl_3$

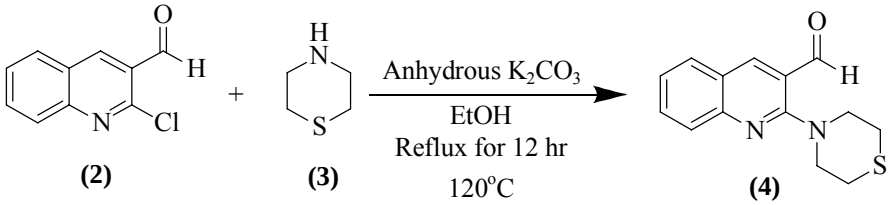
yielded a pure compound (**2**) in high yield.



(1) **(2)**

Step-2: Preparation of 2-thiomorpholinoquinoline-3-carbaldehyde (4)

Thiomorpholine (0.05 mol), 2-chloro-3-formyl-quinoline (0.05 mol) in ethanol (20 mL) and anhydrous K_2CO_3 (3 g) were refluxed at 120°C for 12 hr. The reaction progress was checked by TLC. After completion of the reaction, the reaction mixture was poured into ice cold water. 25 mL water was then added into the reaction mixture. The precipitate was filtered off, washed with water and dried under vacuum (30°C) to give compound (**4)**. Recrytallized from 50% aqueous ethanol. M.P. 182°C.



(2) **(3)** **(4)**

Step-3: General procedure for the preparation of compounds (6a-i)

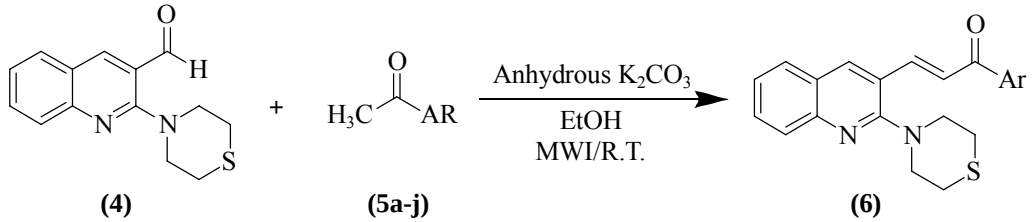
(a) Conventional method

To a solution of 2-thiomorpholinoquinoline-3-carbaldehyde (**4**) (0.01 mol), aryl methyl ketone (**5a-i**) (0.01 mol), basic inorganic catalysts (500 mg) was added in ethanol and mixture was stirred for 24-26 hr at room temperature. The reaction progress was monitored by TLC. After completion of the reaction the reaction mixture was poured into ice cold water and neutralized with dil. HCl. The resulting solid was filtered, dried and recrystallized from ethanol to obtain the compounds **(6a-i)**. The yields and M.P. of the compounds were shown in Table 1.

(b) Microwave irradiation method

To a mixture of 2-thiomorpholinoquinoline-3-carbaldehyde (**4**) (0.01 mol), aryl methyl ketone (**5a-i**) (0.01 mol), basic inorganic catalysts (500 mg) was added and mixture was in ethanol irradiated under microwave at 180 watt for 5-7 min. with 30 sec intervals. The reaction progress was checked by TLC. After completion of the reaction, the reaction

mixture was poured into ice cold water and neutralized with dil.HCl. The resulting solid was filtered, dried and recrystallized from ethanol to obtain the compounds **(6a-i)**. Details of the melting points and yields of the compounds are presented in the Table 1.



(4) **(5a-j)** **(6)**

Table 1: Physical data for chalcones (3a-i)

Compds.	Ar	M.P. (^{o}C)	Reaction time		Yield (%)	
			Conventional (hr)	MWI (min)	Conventional	MWI
6a	Phenyl	155-157	25.0	5.0	70	81
6b	Tolyl	158-160	24.0	5.0	75	83
6c	4-Methoxyphenyl	151-153	24.0	5.0	75	84
6d	4-Nitrophenyl	166-168	26.0	7.0	64	72
6e	4-Chlorophenyl	162-164	26.0	6.0	72	71
6f	4-Bromophenyl	210-212	25.0	6.0	78	78
6g	4-Hydroxyphenyl	180-183	26.0	7.0	74	76
6h	2,4-Dichlorophenyl	167-169	25.0	5.0	70	80
6i	Thienyl	186-188	26.0	5.0	74	86

RESULTS AND DISCUSSION

All the compounds **(6a-i)** were in solid state, yellowish in colour, stable to moisture and temperature. The structures were established by IR, ^{1}H-NMR, ^{13}C NMR and Mass specta.

IR, ^{1}H, ^{13}C-NMR and Mass spectral data of (6a-i)

(*E*)-1-Phenyl-3-(2-thiomorpholinoquinolin-3-yl)prop-2-en-1-one (6a)

IR (KBr): 1659.10 (C=O); 1587.38 (C=C); ^{1}H-NMR ($CDCl_3$): 2.62 (t, 4H, S-CH_2), 3.45 (t, 4H, N-CH_2), 7.39-7.43 (t, 1H, 6-H), 7.52-7.57 (t, 2H, 3′, 5′-H), 7.60-7.69 (d, 3H, 4′,

7, 8-H), 7.75-7.77 (d, 8Hz, 1H, H_α), 7.86-7.88 (d, 8Hz, 1H, H_β), 8.01-8.02 (d, 1H, 5-H), 8.06-8.08 (d, 2H, 2′, 6′-H), 8.29 (s, 1H, 4-H); ^{13}C-NMR ($CDCl_3$): 27.93 (S-CH_2), 52.03 (N-CH_2), 122.74 (C-3), 123.07 (C-10), 124.83 (C-6), 127.85 (C-α), 128.69 (C-8), 128.77 (C-5), 129.11 (C-3′, 5′), 130.63 (C-2′, 6′), 133.26 (C-7), 137.25 (C-4′), 137.90 (C-4), 139.10 (C-1′), 141.93 (C-β), 147.70 (C-9), 159.64 (C-2), 190.20 (C=O); MS: *m/z* = 361 $[M + H]^+$.

(*E*)-3-(2-Thiomorpholinoquinolin-3-yl)-1-(p-tolyl)prop-2-en-1-one (6b)

IR (KBr): 1658.25 (C=O); 1587.12 (C=C); ^{1}H-NMR ($CDCl_3$): 2.46 (s, 3H), 2.62 (t, 4H, S-CH_2), 3.38 (t, 4H, N-CH_2), 7.33-7.36 (d, 2H, 3′, 5′-H), 7.38-7.42 (t, 1H, 6-H), 7.63-7.66 (t, 1H, 7-H), 7.67-7.69 (d, 1H, 8-H), 7.75-7.77 (d, 8Hz, 1H, H_α), 7.84-7.88 (d, 8Hz, 1H, H_β), 7.97-7.99 (d, 1H, 5-H), 8.01-8.04 (d, 2H, 2′, 6′-H), 8.28 (s, 1H, 4-H); ^{13}C-NMR ($CDCl_3$): 21.74 (CH_3); 27.93 (S-CH_2), 50.99 (N-CH_2), 122.87 (C-3′, 5′), 124.25 (C-3), 124.98 (C-10), 127.66 (C-6), 127.82 (C-α), 128.67 (C-8), 129.86 (C-5), 130.55 (C-1′), 135.32 (C-7), 137.19 (C-2′,6′), 138.44 (C-4), 139.04 (C-4′), 141.46 (C-β), 143.99 (C-9), 159.63 (C-2), 189.63 (C=O); MS: *m/z* =375 $[M + H]^+$.

***(E)*-1-(4-Methoxyphenyl)-3-(2-thiomorpholinoquinolin-3-yl)prop-2-en-1-one (6c)**

IR (KBr): 1659.28 (C=O); 1587.31 (C=C); ^{1}H-NMR ($CDCl_3$): 2.68 (t, 4H, S-CH_2), 3.42 (t, 4H, N-CH_2), 3.91 (s, 3H, O-CH_3), 7.00-7.02 (d, 2H, 3′, 5′-H), 7.38-7.41 (t, 1H, 6-H), 7.62-7.66 (t, 1H, 7-H), 7.69-7.73 (d, 8Hz, 1H, H_α), 7.74-7.76 (d, 1H, 8-H), 7.85-7.87 (d, 1H, 5-H), 7.99-8.03 (d, 8Hz, 1H, H_β), 8.08-8.10 (d, 2H, 2′, 6′-H), 8.26 (s, 1H, 4-H); ^{13}C NMR ($CDCl_3$): 27.92 (S-CH_2), 50.97 (N-CH_2), 55.56 (O-CH_3), 113.90 (C-3′, 5′), 113.99 (C-3), 122.86 (C-10), 122.97 (C-6), 124.76 (-C-α), 124.99 (C-8), 127.65 (C-5), 127.79 (C-1′), 130.77 (C-7), 130.94 (C-2′, 6′), 137.13 (C- 4), 141.05 (C- β), 147.60 (C-9), 159.64 (C-4′), 163.65 (C-2); 188.26 (C=O); MS: *m/z* = 391 $[M + H]^+$.

(*E*)-1-(4-Nitrophenyl)-3-(2-thiomorpholinoquinolin-3-yl)prop-2-en-1-one (6d)

IR (KBr): 1658.36 (C=O); 1592.75 (C=C); ^{1}H-NMR (DMSO): 2.90 (t, 4H, S-CH_2), 3.43 (t, 4H, N-CH_2), 7.41-7.44 (t, 1H, 6-H), 7.66-7.69 (t, 1H, 7-H), 7.70-7.72 (d, 1H, 8-H), 7.75-7.79 (d, 8Hz, 1H, H_α), 7.87-7.89 (d, 1H, 5-H), 8.09-8.13 (d, 8Hz, 1H, H_β), 8.20-8.23 (d, 2H, 2′, 6′-H), 8.32 (s, 1H, 4-H), 8.38-8.42 (d, 2H, 3′, 5′-H); ^{13}C-NMR (DMSO): 27.91 (S-CH_2), 50.89 (N-CH_2), 119.02 (C-3), 121.90 (C-10), 123.91 (C-6), 124.90 (C-3′, 5′), 127.11 (C-α), 128.25 (C-8), 129.86 (C-5), 130.95 (C-7), 133.57 (C-2′, 6′), 136.84 (C-4), 138.03 (C-1′), 138.03 (C-β), 141.49 (C-9), 159.38 (C-4′), 170.67 (C-2), 187.96 (C=O); *m/z* = 406 $[M + H]^+$.

(*E*)-1-(4-Chlorophenyl)-3-(2-thiomorpholinoquinolin-3-yl)prop-2-en-1-one (6e)

IR (KBr): 1659.72 (C=O); 1591.32 (C=C); ^{1}H-NMR ($CDCl_3$): 2.62 (t, 4H, S-CH_2), 3.40 (t, 4H, N-CH_2), 7.39-7.42 (t, 1H, 6-H), 7.50-7.52 (d, 2H, 3′, 5′-H); 7.64-7.66 (t, 1H, 7-H); 7.68 (d, 1H, 8-H); 7.75-7.77 (d, 8Hz, 1H, H_α); 7.86-7.88 (d, 8Hz, 1H, H_β); 8.01-8.03 (d, 2H, 2′, 6′-H); 8.06 (d, 1H, 5-H); 8.28 (s, 1H, 4-H); ^{13}C-NMR ($CDCl_3$): 27.90 (S-CH_2), 51.05 (N-CH_2), 122.30 (C-3), 124.92 (C-10), 127.70 (C-6), 127.86 (C-α), 129.00 (C-8), 129.04 (C-5), 129.14 (C-3′, 5′), 129.99 (C-7), 130.75 (C-2′, 6′), 136.18 (C-4), 137.35 (C-1′), 139.54 (C-4′), 142.37 (C-β), 147.75 (C-9), 159.60 (C-2), 188.68 (C=O); *m/z* = 395 $[M + H]^+$.

(*E*)-1-(4-Bromophenyl)-3-(2-thiomorpholinoquinolin-3-yl)prop-2-en-1-one (6f)

IR (KBr): 1657.15 (C=O); 1591.98 (C=C); ^{1}H-NMR ($CDCl_3$): 2.67 (t, 4H, S-CH_2), 3.41 (t, 4H, N-CH_2), 7.39-7.43 (t, 1H, 6-H), 7.64-7.67 (t, 1H, 7-H), 7.68-7.69 (d, 1H, 8-H), 7.70 (d, 1H, 3′, 5′-H), 7.75-7.78 (d, 8Hz, 1H, H_α), 7.87-7.89 (d, 8Hz, 1H, H_β), 7.93-7.96 (d, 2H, 2′, 6′-H), 8.03-8.07 (d, 1H, 5-H), 8.29 (s, 1H, 4-H); ^{13}C-NMR ($CDCl_3$): 27.90 (S-CH_2), 51.06 (N-CH_2), 122.31 (C-3), 122.53 (C-10), 124.89 (C-6), 124.92 (C-α), 127.63 (C-8), 127.86 (C-3′, 5′), 128.26 (C-5), 130.02 (C-4′), 130.81 (C-7), 132.02 (C-2′, 6′), 132.08 (C-4), 136.60 (C-1′), 142.41 (C-9), 159.56 (C-2), 188.80 (C=O); *m/z* = 439 $[M + H]^+$.

(*E*)-1-(4-Hydroxyphenyl)-3-(2-thiomorpholinoquinolin-3-yl)prop-2-en-1-one(6g)

IR (KBr): 1649.74 (C=O); 1592.47 (C=C); ^{1}H-NMR (DMSO): 2.67 (t, 4H, S-CH_2), 3.41 (t, 4H, N-CH_2), 7.00-7.03 (d, 2H, 3′, 5′-H), 7.39-7.42 (t, 1H, 6-H), 7.62-7.66 (t, 1H, 7-H), 7.68-7.72 (d, 8Hz, 1H, H_α), 7.74-7.76 (d, 1H, 8-H), 7.84-7.86 (d, 1H, 5-H), 7.98-8.02 (d, 8Hz, 1H, H_β), 8.06-8.08 (d, 2H, 2′, 6′-H), 8.26 (s, 1H, 4-H); ^{13}C-NMR (DMSO): 27.90 (S-CH_2), 51.05 (N-CH_2), 122.30 (C-8′), 122.52 (C-3), 124.87 (C-10), 124.92 (C-6), 127.70 (C-6′), 127.86 (3′, 8), 129.00 (C-2′), 129.04 (C-5), 129.09 (C-9′), 129.14 (C-7), 129.91 (C-5′), 129.99 (C-10′), 130.75 (C-4′), 136.18 (C-7′), 137.35 (C-4), 139.54 (C-1′), 142.37 (C-β), 147.75 (C-9), 159.60 (C-2), 188.68 (C=O); *m/z* = 361 $[M + H]^+$.

(*E*)-1-(2,4-Dichlorophenyl)-3-(2-thiomorpholinoquinolin-3-yl)prop-2-en-1-one(6h)

IR (KBr): 1659.72 (C=O); 1591.32 (C=C); ^{1}H-NMR ($CDCl_3$): 2.62 (t, 4H, S-CH_2), 3.40 (t, 4H, N-CH_2), 7.39-7.42 (t, 1H, 6-H), 7.50-7.52 (d, 2H, 3′, 5′-H); 7.64-7.66 (t, 1H, 7-H); 7.68 (d, 1H, 8-H); 7.75-7.77 (d, 8Hz, 1H, H_α); 7.86-7.88 (d, 8Hz, 1H, H_β); 8.01-8.03 (d, 1H, 6′-H); 8.06 (d, 1H, 5-H); 8.28 (s, 1H, 4-H); ^{13}C-NMR ($CDCl_3$): 27.90 (S-CH_2), 51.05 (N-CH_2), 122.30 (C-3), 124.92 (C-10), 127.70 (C-6), 127.86 (C-α), 129.00 (C-8), 129.04 (C-5), 129.14 (C-3′, 5′), 129.99 (C-7), 130.75 (C-2′, 6′), 136.18 (C-4), 137.35 (C-1′), 139.54 (C-4′), 142.37(C- β), 147.75 (C-9), 159.60 (C-2), 188.68 (C=O); *m/z* = 430 $[M + H]^+$.

(*E*)-3-(2-Thiomorpholinoquinolin-3-yl)-1-(thiophen-2-yl)prop-2-en-1-one (6i)

IR (KBr): 1656.27 (C=O); 1592.83 (C=C); ^{1}H-NMR ($CDCl_3$): 2.67 (t, 4H, S-CH_2), 3.42 (t, 4H, N-CH_2), 7.22-7.26 (d, 2H, 3′, 5′-H), 7.39-7.43 (t, 1H, 4′-H), 7.58-7.63 (t, 1H, 6-H), 7.66-7.68 (t, 1H, 7-H), 7.76-7.78 (d, 1H, 8-H), 7.86-7.88 (d, 8Hz, 1H, H_α), 7.92-7.96 (d, 8Hz, 1H, H_β), 8.05-8.08 (d, 1H, 5-H), 8.27 (s, 1H, 4-H); ^{13}C-NMR ($CDCl_3$): 27.95 (S-CH_2), 51.00 (N-CH_2), 122.54 (C-10), 124.83 (C-6), 127.68 (C-α), 127.84 (C-8), 128.40 (C-4′), 130.67 (C-7), 131.97 (C-4), 134.25 (C-5′), 137.50 (C-3′), 141.21 (C-2′), 145.32 (C-β), 147.69 (C-9), 159.62 (C-2), 180.74 (C=O); *m/z* = 367 $[M + H]^+$.

Biological activity

The newly synthesized compounds **(6a-i)** were screened for their antibacterial activity against Gram-positive bacteria *viz. Staphylococcus aureus* and *basillus* and Gram negative bacteria *viz. Escherichia coli* and *klebsiella* at *i.e.* 100, 50 and 25 µg using ditch dilution methods. The test organism was a two hour culture of *Escherichia coli, klebsiella* and *Staphylococcus aureus* and *basillus* incubated and grown in peptone-water medium (temp. 37^{o}C). DMF was used as solvent control, which did not show any zone of inhibition. Muller-Hilton agar medium was used as culture medium. The culture plates were incubated at 37^{o}C for 24 hrs. Out of three concentrations chosen, the best result was obtained 25 µg and hence, this was optimum concentration. All the compounds were found to show strong activity against Gram-positive bacteria *viz. Staphylococcus aureus* and *basillus.* In case of Gram negative bacteria *viz. Escherichia coli* and *klebsiella*, some compounds were found to be inactive.

The results are given in Table 2.

Table 2: Activity of the synthesized compounds: Antimicrobial studies of compounds (6a-i) at 50 mg/mL

Compounds	Antibacterial activity, zone of inhibition (mm)			
	S. Aureus	***E. coli***	***Bacillus***	***Klebsiella***
Gentamycin	15	20	17	15
6a	06	-	06	-
6b	05	-	07	-
6c	07	-	-	-
6d	06	-	08	-

Cont…

Compounds	Antibacterial activity zone of inhibition (mm)			
	S. Aureus	***E. coli***	***Bacillus***	***Klebsiella***
6e	08	06	07	07
6f	08	07	08	08
6g	07	08	08	08
6h	05	-	06	-
6i	06	06	07	-

CONCLUSION

In this synthetic work, the compounds **(6a-i)** were synthesized by conventional method and microwave irradiation method. Among these, microwave irradiation method is an easy, high yielding, convenient and green method. The process proved to be a simple, environmentally friendly technique with high yields and high rate of acceleration was achieved in performing the reaction in microwave irradiation technique. These compounds were characterized on the basis of IR, ^{1}H-NMR, ^{13}C-NMR and Mass spectra.

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