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Microwave Assisted Synthesis of 3-(2-chloroquiolin-3-yl)-1-substituted phenyl prop-2-en-1-ones Using K_2CO_3 as a Mild, Cheap and Inexpensive Catalyst

Vandana Tiwari, Parvez Ali, Jyotsna Meshram*

*** Department of Chemistry, Rashtasant Tukadoji Maharaj, Nagpur University,**

Nagpur, M.S.,India 440033

Corres.author: vandanachemie@gmail.com,drjsmeshram@rediffmail.com

Abstract : In this communication, we have reported the synthesis of novel 3-(2-chloroquiolin-3-yl)-1-substituted phenyl prop-2-en-1-ones by Claisen–Schmidt condensation using microwave assisted solid phase, solvent free protocol Using K_2CO_3 as a mild, cheap and inexpensive catalyst instead of normal bases like NaOH, KOH which makes the process hazardous to health. All the synthesized compounds were well characterised by spectral analysis. Thus the process seems to be eco-friendly, economic, easy and thus constitute a part of e-chemistry.
Keywords: Claisen–Schmidt condensation, chalcones, microwave, solid phase.

Introduction

Over the years various innovative methods have been devised to speed up the chemical reactions. In these environmentally conscious days the development of technology is directed towards environmentally sound and ecofriendly methods. The usage of microwave energy to accelerate the organic reactions is of increasing interest and offers several advantages over conventional heating techniques[1]. Synthesis of the molecules which normally requires a long time can be achieved conveniently and rapidly in microwave oven. Less reaction time, easy work up and cleaner products are the major advantages of microwave heating. Furthermore the reactions can be carried out under solvent free conditions which hold a strategic position as the solvents are often very toxic, expensive, problematic to use. Solvent free condition is especially suitable for microwave activation. Thus the use of microwave energy for the synthesis of organic compounds forms a part of green chemistry.

Chalcones having an α, β unsaturated carbonyl group are one of the important biocides and versatile synthons for various chemical transformations. Most of the chalcones are highly biologically active with a number of pharmacological and medicinal applications[2]. Chalcones have been used as anti HIV agents[3], cytotoxic agents with antiangiogenic activity[4] antimalarials[5], anti-inflammatory[6] and anti-tumour agents [7]. Keeping in view the advantages of microwave heating and the usage of chalcones as natural biocides, we have carried out the synthesis of some substituted quinoline chalcones by Claisen-Schimdt condensation in the present investigation. This reaction is generally carried out in presence of base like NaOH or KOH which are harmful, toxic and polluting. Therefore in the present investigation we have used anhydrous K_2CO_3 as the condensing agent which is cheap, non-toxic and easy to use. Furthermore the reaction can be easily carried out under solvent free condition under microwave irradiation so as to minimize the pollution. Variously substituted acetophenones were condensed with aromatic quinoline aldehydes in presence of anhydrous K_2CO_3 to afford the desired chalcones in 85-90% yields under

microwave irradiations. The reaction was completed within 3-5-minutes.

Experimental

General

The solvents and reagents used in the synthetic work were of analytical grade obtained from Qualigens India and were purified by distillation or crystallization where necessary and their boiling or melting points were compared with the available literature values. Melting points were determined in open capillaries and are uncorrected. ^{1}H-NMR spectra were recorded on a Perkin Elmer FT-NMR Cryo-magnet Spectrometer 400 MHz (Bruker) instrument using tetramethylsilane (TMS) as an internal standard and DMSO-d_6 as a solvent. Chemical shifts are given in parts per million (ppm). Infrared spectra were recorded on Schimadzu-IR Prestige 21. Mass spectra were recorded on a Waters Micromass Q-T of Micro spectrometer. The reactions were monitored and the purity of products was checked out on pre-coated TLC plates (Silica gel 60 F254, Merck), visualizing the spots under ultraviolet light and iodine chamber.

Conventional method for the synthesis of Chalcones 4 (a-j):

To the solution of (0.01 mol) of 2-chloroquinoline -3-carbaldehyde in 5 mL of methanol, freshly prepared 2N methanolic NaOH solution (30ml) was added in ice cold condition and stirred for 10 mins. To this (0.01mol) of appropriate ketones was added and the reaction mixture was stirred at room temperature for 24h. The reaction mixture was cooled on an ice bath and neutralized with dilute hydrochloric acid. The precipitate appeared was separated by filtration and washed three times with 20 ml distilled water to give the crude product. The product so obtained was recrystallized from methanol**.** The purity of the products was checked on TLC (Merck Silica gel 60F254) by using mixture of ethyl acetate and hexane as mobile phase.

Microwave method for the synthesis of Chalcones 4 (a-j):

The reaction was carried out in domestic microwave oven (Samsung M1630N, output 600watts, frequency 2450 MHz.). Substituted acetophenone (0.01mol), 2-chloroquinoline -3-carbaldehyde (0.01mol) and anhydrous K_2CO_3 were thoroughly mixed to form a thick paste. The paste was air dried and the residual mass was subjected to microwave irradiation for 3-5minutes. After completion of reaction the contents were dissolved in ethanol. Inorganic material was filtered off and the solvent was evaporate under vaccum to get the desired chalcones in 80-90% yields. The purity of the products was checked on TLC (Merck Silica gel 60F254) by using mixture of ethyl acetate and hexane as mobile phase.

Data

3-(2-chloroquiolin-3-yl)-1-phenylprop-2-en-1-one (4a)

Prepared by above method from 3 (0.01mol) and acetophenone (0.01 mol); Yield: 81%; *R*f = 0.44 in EtOAc/hexane, 3:7; yellow solid. mp:132-140^{0}C; MS((M^+):, *caltd.*: 294.753, *observed:* 294.062; FTIR (cm^{-1}):1732 (C=O), 1639 (CH=CH), 853 (C-Cl); ^{1}H NMR (400 MHz, DMSO *d*6) δ/ppm 7.53 (1H, d, H_α), 8.52 (1H, d, H_β), 7.40-8.31 (m, 10H, aromatic); Anal. Calcd: $C_{18}H_{12}ClNO$: C,73.54 ; H ,4.17; N,4.75.Found: C,73.60 ; H ,4.24; N ,4.78.

3-(2-chloroquinolin-3-yl)-1-(2,4-dichorophenyl)-) prop-2-en-1-one (4b)

Prepared by above method from **3** (0.01mol) and 2,4-dichloroacetophenone (0,01 mol); Yield: 87%, *R*f = 0.65 in EtOAc/hexane, 3:7. Pale yellow solid.mp:135-138^{0}C; MS (M^+):, *caltd.*: 360.682, *observed:* 360.981; FTIR (cm^{-1}): 1732 (C=O), 1639 (CH=CH), 853 (C-Cl); ^{1}H NMR (400 MHz, DMSO *d*6) δ/ppm : 7.65 (1H, d,H_α), 8.51 (1H, d, H_β), 7.34-8.32 (m, 8H, aromatic).Anal.Calcd: $C_{18}H_{10}Cl_3NO$: C,59.60 ; H ,2.76; N ,3.81.Found: C,59.65 ; H ,2.79; N,3.86.

3-(2-chloroquinolin-3-yl)-1-(3,4-dichlorophenyl)prop-2-en-1-one (4c)

Prepared by above method from **3** (0.01mol) and 3,4-dichloroacetophenone (0.01mol); Yield: 83%, *R*f = 0.61 in EtOAc/hexane, 3:7; Pale yellow solid. mp: 145-148^{0}C; MS (M^+): *caltd.*: 360.072, *observed:* 360.214; FTIR (cm^{-1}): 1730 (C=O), 1643 (CH=CH), 853 (C-Cl); ^{1}H NMR (400 MHz, DMSO *d*6) δ/ppm 7.70 (1H, d,H_α), 8.55 (1H, d,H_β), 6.99-8.25 (m, 8H, aromatic)., Anal. Calcd: $C_{18}H_{10}Cl_3NO$: C, 59.40 ; H ,2.76; N 3.80.Found: C, 59.45 ; H ,2.78; N 3.88.

3-(2-chloroquinolin-3-yl)-1-p-tolyl prop-2-en-1-one (4d)

Prepared by above method from **3** (0.01mol) and 4-methyl acetophenone (0.01mol); Yield: 80%, *R*f = 0.56 in EtOAc/hexane, 3:7; Yellow crystalline solid.mp: 140-148 ^{0}C; ESI-MS (M^+): *caltd.*: 307.107, *observed:* 307.184; FTIR (cm^{-1}): 1728 (C=O), 1643 (CH=CH), 853 (C-Cl); ^{1}H NMR (400 MHz, DMSO *d*6) δ/ppm 2.38 (3H, s, CH_3), 7.54 (1H, d, H_α), 8.59 (1H, d, H_β), 7.29-8.33 (m, 9H, aromatic)., Anal. Calcd: $C_{19}H_{14}ClNO$: C, 74.12 ; H ,4.56; N 4.49.Found: C, 74.15 ; H ,4.58; N 4.18.

3-(2-chloroqunolin-3-yl)-1-o-tolyl prop-2-en-1-one (4e)

Prepared by above method from **3** (0.01mol) and 2-methyl acetophenone (0.01mol); Yield: 85%, *R*f = 0.51 in EtOAc /hexane, 3:7; Yellow crystalline solid. mp: 132-140^{0}C; ESI-MS (M^+): *caltd.*: 307.128, *observed:* 307.161; FTIR(cm^{-1}):1728 (C=O), 1643 (CH=CH), 853 (C-Cl); ^{1}H NMR (400 MHz, DMSO *d*6) δ/ppm 2.38 (3H, s, CH_3), 7.54 (1H, d, H_α), 8.51 (1H, d, H_β), 7.29-8.27 (m, 9H, aromatic).,Anal. Calcd: $C_{19}H_{14}ClNO$: C, 74.11 ; H ,4.56; N 4.49.Found: C,74.15 ; H ,4.58; N 4.18.

3-(2-chloroquinolin-3-yl)-1-(4-bromophenyl) prop-2-en-1-one (4f)

Prepared by above method from **3** (0.01mol) and 4-Bromoacetophenone (0.01mol); Yield : 84%; *R*f = 0.59 in EtOAc/hexane, 3:7; Pale yellow crystalline solid. mp: 146-150 ^{0}C; ESI-MS (M+Na): *caltd.*: 393.132, *observed:* 393.148; FTIR (cm^{-1}): 1728 (C=O), 1643 (CH=CH), 853 (C-Cl) , 588 (C-Br) ;^{1}H NMR (400 MHz, DMSO *d*6) δ/ppm 7.54 (1H, d, H_α), 8.53 (1H, d, H_β), 7.43-8.31 (m, 9H, aromatic).Anal.Calcd: $C_{18}H_{11}ClBrNO$: C,58.01 ; H ,2.96; N,3.74.Found: C,58.04 ; H ,4.98; N,3.78.

3-(2-chloroquinolin-3-yl)-1-(2-bromophenyl) prop-2-en-1-one (4g)

Prepared by above method from **3** (0.01mol) and 2-Bromoacetophenone (0.01mol); Yield: 86%, *R*f = 0.58 in EtOAc/hexane,3:7; Yellow crystalline solid. mp: 166-170^{0}C; ESI-MS (M^+): *caltd.*: 370.123, *observed:* 370.190. FTIR (cm^{-1}):1728 (C=O), 1643 (CH=CH), 853 (C-Cl) , 588 (C-Br); ^{1}H NMR (400 MHz, DMSO *d*6) δ/ppm 7.54 (1H, d, H_α), 7.90 (1H, d, H_β), 7.43-8.32 (m, 9H, aromatic).Anal.Calcd: $C_{18}H_{11}ClBrNO$: C,58.01 ; H ,2.96; N ,3.74.Found: C,58.04 ; H ,4.98; N,3.78.

3-(2-chlroquinlin-3-yl)-1-(3-nitrophenyl) prop-2-en-1-one (4h)

Prepared by above method from **3** (0.01mol) and 3-nitroacetophenone (0.01mol); Yield: 80%, *R*f = 0.54 in EtOAc/hexane, 4:6; Pale yellow solid. mp: 145-150 ^{0}C; ESI-MS (M^+): *caltd.*: 338.012, *observed:*338.966; FTIR (cm^{-1}): 1732 (C=O), 1645 (CH=CH), 853 (C-Cl) , 1589(-NO_2); ^{1}H NMR (400 MHz, DMSO *d*6) δ/ppm 7.53 (1H, d, H_α), 8.51 (1H, d, H_β), 7.23-8.10 (m, 9H, aromatic).Anal.Calcd: $C_{18}H_{11}ClN_2O_3$: C,68.71 ; H ,3.26; N,8.24.Found: C,63.84 ; H ,3.28; N,8.28.

3-(2-chloroquinolin-3-yl)-1-(3,4,5-trimethoxyphenyl) prop-2-en-1-one (4i)

Prepared by above method from **3** (0.01mol) and 3,4.5-trimethoxyacetophenone (0.01mol); Yield: 87%, *R*f = 0.48 in EtOAc/hexane, 3:7; Yellow crystalline solid. mp: 174-175 ^{0}C; ESI-MS (M^+): *caltd.*: 383.132, *observed:* 383.401; FTIR (cm^{-1}): 1732 (C=O), 1645 (CH=CH), 853 (C-Cl) ; ^{1}H NMR (400 MHz, DMSO *d*6) δ/ppm 7.53 (1H, d, H_α), 8.57 (1H, d, H_β), 3.80 (s, 6H, CH_3), 3.64 (s, 3H, CH_3), 7.43-8.28 (m, 7H, aromatic).Anal.Calcd: $C_{21}H_{18}ClNO_4$: C,65.71 ; H ,4.71; N,3.64.Found: C,65.84 ; H ,4.78; N,3.68.

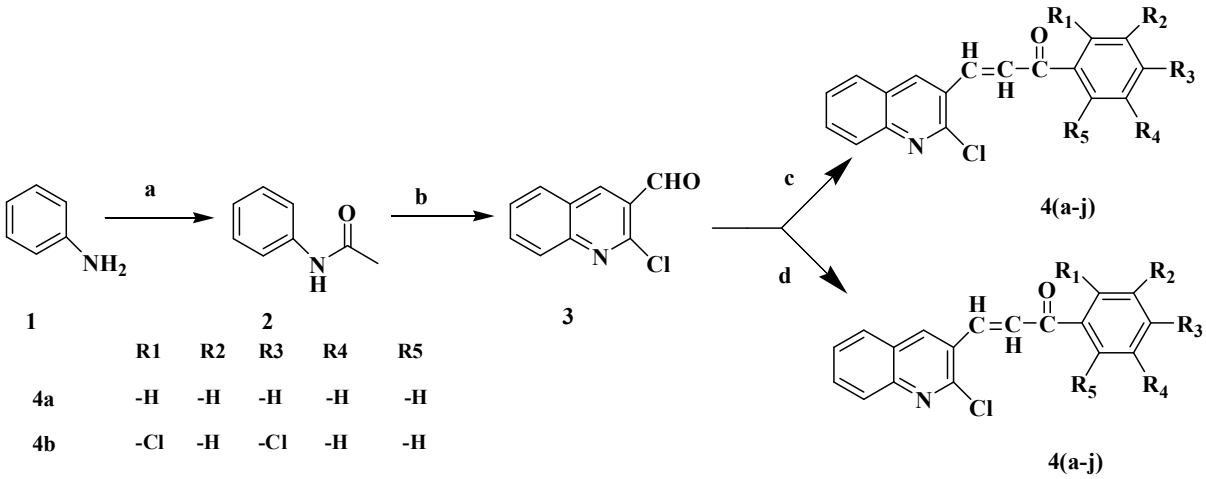
3-(2-chloroquinolin-3-yl)-1-(5-bromo-2-methoxyphenyl)prop-2-en-1-one(4j)

Prepared by above method from **3** (0.01mol) and 2-methoxy-5-bromoacetophenone (0.01mol); Yield: 81%, *R*f = 0.63 in EtOAc/hexane, 4:6; Yellow solid. mp: 160-168^{0}C; ESI-MS (M^+):, *caltd.*: 400.850, *observed:* 400.991; FTIR (cm-^{1}): 1736 (C=O), 1645 (CH=CH), 853 (C-Cl) ,588 (C-Br); ^{1}H NMR (400 MHz, DMSO *d*6) δ/ppm 7.53 (1H, d, H_α), 8.57 (1H, d, H_β), 3.73 (s, 3H, CH_3), 7.40-8.31 (m, 7H, aromatic).Anal.Calcd: $C_{20}H_{14}ClBrNO_2$: C,56.61 ; H ,3.21; N,3.44.Found: C,56.64 ; H ,3.25; N,3.46.

Results and Discussion

Claisen-Schimdt condensation is a versatile method for the preparation of α, β-unsaturated carbonyl compounds (Chalcones). The reaction is generally carried in presence of aqueous alkali [9-13]. The concentration of the alkali generally lies between 10-60%. Other condensing agents which have been used for this reaction include alkali metal oxides, [14] magnesium tert.- butoxide [15] potassium carbon compounds(KC_8) [16], boric anhydride [17], organo-cadmium compounds[18], and lithium iodide[19] which are quite expensive and require a lot of precautions during their use. In the present investigation we have carried out the condensation of 2-chloro Quinoline-3-carboxaldehyde and aromatic ketones in presence of anhydrous potassium carbonate as shown in **Scheme 1**. In comparison to above mentioned condensing agents it is non toxic, non expensive and easy to use reagent. Furthermore its use in presence on microwave irradiation makes the process eco-friendly and economic and makes a new path in green chemical transformation. In comparison to the conventional method and reagents the yields obtained are higher as shown in **Table 1** and **Fig 1.**

Scheme I



1 **2** **3**

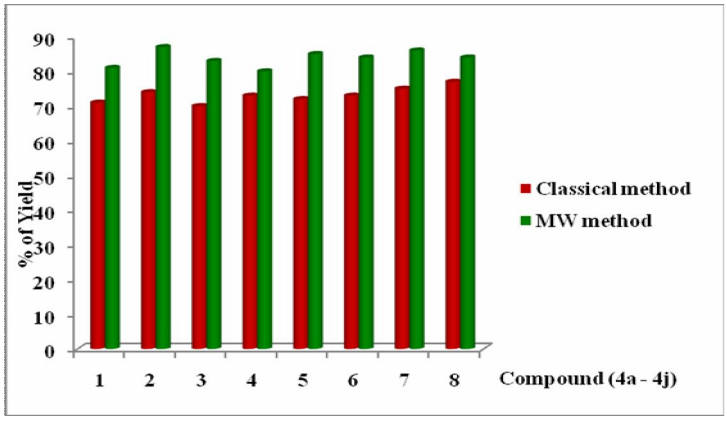
	R1	R2	R3	R4	R5
4a	-H	-H	-H	-H	-H
4b	-Cl	-H	-Cl	-H	-H
4c	-H	-Cl	-Cl	-H	-H
4d	-H	-H	$-CH_3$	-H	-H
4e	$-CH_3$	-H	-H	- H	-H
4f	-H	-H	-Br	-H	-H
4g	-Br	-H	-H	-H	-H
4h	-H	$-NO_2$	-H	-H	-H
4i	-H	$-OCH_3$	$-OCH_3$	$-OCH_3$	-H
4j	$-OCH_3$	-H	-H	-Br	-H

Reagents: a) Ac2O, AcOH, reflux, 2 h. b) DMF, POCl3 (3: 12), reflux, 6 h, 80-90 ^{0}C. c) substituted acetophenone, NaOMe,MeOH, 20% NaOH, stir, 24 h. d)substituted acetophenone, K_2CO_3 ,under microwave

Table 1: - Time taken & %yield for compounds 4(a-j)

Comp.	Conventional Method		Microwave Method	
	Time (hr)	% Yield	Time (min)	% Yield
4a	21	71	2	81
4b	23	74	3	87
4c	22	70	2	83
4d	24	73	2	80
4e	20	72	3	85
4f	22	73	3	84
4g	24	75	2	86
4h	21	77	2	84
4i	23	72	2	80
4j	22	71	3	87

Fig 1- Plot between % yield of compound by classical and microwave method.



The identity of the products obtained was confirmed on the basis of their elemental analysis and spectral data. The IR spectra of these compound gave prominent peaks at 1740-1730 cm^{-1}, (C=O), 3100—3000cm^{-1} (C-H stret.), 1639-1641 cm^{-1} (CH=CH) and 853cm^{-1} (Cl stret.). ^{1}H-NMR spectra of chalcones gave double doublet for vinylic protons at δ7.6-8.3 and a multiplet for aromatic protons at δ7.8-8.0. The mass spectra of these compounds gave molecular ion peaks corresponding to their molecular masses.

Conclusion

In conclusion, we have developed a K_2CO_3-catalyzed, simple, solvent-free, cost effective, and environmentally benign technique for the synthesis of Quinoline chalcones. This reaction is scalable to multigram scale. These compounds have been synthesized in high yield by using K_2CO_3 and avoiding the use of any solvent under microwaves.

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