Research Article

Comparative Study on Conventional and Ultrasound Irradiation Promoted Synthesis of 2, 3-Disubstitutedquinoxaline Derivatives

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Abstract

A series of ten chalcone-substituted quinoxalines (4a-e), (3a-e) starting from 1-(phenylquinoxalin-2-yl)ethanone and 1-(3-methylquinoxalin-2-yl)ethanone have been synthesized using conventional heating and ultrasound-assisted methods. Furthermore, novel of five quinoxaline derivatives, including pyrazoline, isoxazole, pyrimidin-2-one, *N*-acylpyrazoline and pyridin-2-one moieties were also prepared from the reaction of chalcone compound 4a with different cyclization reagents using the same strategy. The structures of all synthesized compounds were established on the basis of FT-IR, ^{1}H-NMR and ^{13}C-NMR. The ultrasonic irradiation method provides several advantages over conventional heating method, including shorter reaction times (30-90 min.) and good percentage yields (65% - 88%), comparing with conventional protocol (5 to 20 hrs. with 30% to 55% reaction yields).

Keywords: ultrasonic, chalcone, quinoxaline, chalcone.

الخلاصة:

لقد تم تحضير سلسلة من عشر مشتقات الكوينوكزولين الجديدة أبتداءا من 1-فنيل كوينوكزولين-2-أيثانون و 3-مثيل كوينوكزولين-2-أيثانون وبأستخدام طريقتين هما طريقة التسخين الاعتيادية وتقنية استخدام موجات فوق الصوتية. أضافة الى ذلك تم تحضير خمس مشتقات أخرى جديدة من الكوينوكزولين تحتوي على حلقات البايروزين, أيزوكزازول, بيرمدين2-ون, وذلك من تفاعل مركب الجالكون مع كواشف مختلفة للغلق وبأستخدام نفس التقنيتين أعلاه. تم تشخيص جميع المركبات المحضرة بأستخدام تقنيات.FT-IR, ^{1}H-NMR and ^{13}C-NMR.

وأظهرت طريقة الأشعة فوق الصوتية فوائد عديدة مقارنة مع طريقة التسخين الاعتيادية, منها تقليل سرعة التفاعل الى (30-90 دقيقة), وايضا زيادة حصيلة التفاعل الى (65%-88%) مقارنة مع طريقة التسخين الاعتيادية (5-20 ساعة) مع (30-55%) حصيلة التفاعل.

Introduction

The synthesis and chemistry of quinoxaline and its derivatives have attracted considerable attention in the past fifteen years [1] [2]. Quinoxalines are important nitrogen containing heterocyclic compounds of various biological interesting properties. Substituted quinoxalines constitute the building blocks of wide and diverse spectrum of pharmacological properties such as antitumor [3], antimicrobial [4], and anti-inflammatory activities [5]. In addition the quinoxaline derivatives are also associated with application in dyes [6], organic semiconductors [7] and efficient electron luminescent materials [8]. Ultrasound-assisted organic synthesis (UAOS) is a green synthetic technique that has attracting worthy research activity within the synthetic and medicinal community during the

past two decades [9] [10] [11]. Nowadays, UAOS has been utilized, not only to lessening reaction times, but also for getting higher product yields and purity, and improved levels of selectivity in a large assortment of Multifunctionalized heterocycles. Compare with conventional heating methods, ultrasonic irradiation technique is more adequate, efficient, and facilely controlled. A several synthetic reactions can be carried out in milder conditions, excellent yield and shorter time under this method [12] [13] [14] [15]. The present paper described the synthesis of some chalcone-substituted quinoxalines and some of related cyclic derivatives carrying of pyrazoline, isoxazole, pyrimidin-2-one, N-acylpyrazoline and pyridin-2- one moiety, under conventional and ultrasonic irradiation condition with a comparative study.

Materials and Methodology

All the chemicals and solvents used in this study were reagent grade and they are available from Sigma-Aldrich and Alfa-Aesar companies. Melting points were determined on a Micro heating table HMK 67/1825 Kuestner (Büchi Apparatus), Leitz Labolux 12 Pol with heating table Mettler FP 90 and uncorrected. The FT-IR spectra were obtained using Nicolet 205 FT-IR, Nicolet Protége 460 FT-IR. The ^{1}H-NMR spectra were recorded on a Bruker AVANCE 250 II (built 2006), Bruker AVANCE 300 II (built 2007) spectrometry, using $CDCl_3$ as solvent and TMS as internal standard. Sonocation was performed in an ELO-150 ultrasonic cleaner with a frequency of 46 KHz and a normal power of 200 W. Thin layer chromatography (TLC) was carried out on Merck Kieselgel 60 F254 on aluminium foil from Macherey-Nagel. Detection was carried out under UV light λ_{max} at 254 nm and λ_{max} at 365 nm. Solutions were evaporated under diminished pressure unless otherwise stated.

Preparation of chalcone-substituted quinoxalines (3_{a-e}), (4_{a-e}):

Conventional heating method:

A mixture of 1-(3-methylquinoxalin-2-yl)ethanone or 1-(phenylquinoxalin-2-yl) ethanone (1 mmole), aromatic aldehyde (1 mmole) in 1-butanol (20 ml) was treated with $LiOH.H_2O$ (4.2 mg, 0.1 mmole, 10 mol %). A mixture was refluxed for about 5h. The progress of the reaction was monitored by TLC using heptane: ethylacetate as a developer. The reaction mixture was poured over crushed ice and acidified with dilute HCl and extracted with dichloromethane (3 x 5ml). The combine DCM extracts were washed with brine solution (5ml) and dried over anhydrous magnesium sulfate, and concentrated in vacuo. The residue was purified by column chromatography (flash silica gel, heptane/EtOAc).

Ultrasound-assisted method:

A mixture of 1-(3-methylquinoxalin-2-yl)ethanone or 1-(phenylquinoxalin-2-yl) ethanone (1 mmole), aromatic aldehyde (1 mmole) in 1-butanol (5 ml) was treated with $LiOH.H_2O$ (4.2 mg, 0.1 mmole, 10 mol %). They was heated and irradiated in an ultrasonic bath at 60 C^o for time given in Table 1. TLC monitored the completion of the reaction. The reaction mixture was poured over crushed ice, acidified with dilute HCl, extracted with dichloromethane and dried over anhydrous magnesium sulfate. The crude product was purified by column chromatography (flash silica gel, heptane/EtOAc).

(E)-3-(4-bromophenyl)-1-(3-methylquinoxalin-2-yl)prop-2-en-1-one (**3a**): M.p. 210 ^{o}C; IR (KBr) [υ, cm^{-1}]: 3086 $(C\text{-}H)_{arom}$, 2929, 2860 $(C\text{-}H)_{alph}$, 1651 (C=O), 1585 (C=C); ^{1}H-NMR (300 MHz, $CDCl_3$) δ : 2.38 (s, 3H, CH_3), 6.68 (d, 1H, *J*=15.8 Hz, CH_{vinyl}), 6.95 (d, 2H, *J*=8.1 Hz, ArH), 7.25 (d, 2H, *J*=8.2 Hz, ArH), 7.32-7.40 (m, 1H, CH_{vinyl}), 7.49 (d, 1H, *J*=8.4 Hz, ArH), 7.57-7.63 (m, 1H, ArH), 7.91 (d, 1H, *J*=8.3 Hz, ArH), 8.15 (d, 1H, *J*=8.0 Hz, ArH);^{13}C-NMR (75.5 MHz, $CDCl_3$) δ: 20.9 (CH_3), 121.7, 122.2, 123.5, 123.6, 125.7, 126.7, 128.4, 128.9, 129.3, 129.7 (CH), 130.5, 135.6, 136.0, 142.0, 145.2, 145.8 (C), 200.3 (CO).

(E)-1-(3-methylquinoxalin-2-yl)-3-(naphthalen-1-yl)prop-2-en-1-one (**3b**): M.p. 215 ^{o}C; IR (KBr) [υ, cm^{-1}]: 3075 $(C\text{-}H)_{arom}$, 2935, 2865 $(C\text{-}H)_{alph}$, 1655 (C=O) ,1575 (C=C); ^{1}H-NMR (300 MHz, $CDCl_3$) δ : 2.38 (s, 3H, CH_3), 6.68 (d, 1H, *J*=15.5 Hz, CH_{vinyl}), 7.05-7.14 (m, 2H,

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ArH), 7.28 (d, 1H, *J*=8.1 Hz, ArH), 7.30-7.45 (m, 3H, CH_{vinyl}, 2 ArH), 7.50-7.70 (m, 4H, ArH), 8.05 (d, 2H, *J*=8.2 Hz, ArH); ^{13}C-NMR (75.5 MHz, $CDCl_3$) δ: 28.8 (CH_3), 120.8, 122.0, 124.4, 125.0, 127.7, 127.9, 128.0, 129.4, 129.6, 129.8, 130.4, 130.9 (CH), 133.5 (C), 135.1 (CH), 135.6, 136.6, 137.7, 140.4, 141.9, 144.5 (C), 200.4 (CO).

(E)-3-(3,4-dimethoxyphenyl)-1-(3-methylquinoxalin-2-yl)prop-2-en-1-one (**3c**): M.p. 220 ^{o}C; IR (KBr) [υ, cm^{-1}]: 3086 (C-H)$_{arom}$, 2929, 2860 (C-H)$_{alph}$, 1651 (C=O), 1585 (C=C); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.36 (s, 3H, CH_3), 3.63 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 6.68 (d, 1H, *J*=15.8 Hz, CH_{vinyl}), 7.11 (d, 2H, *J*=8.5 Hz, ArH), 7.20 (d, 1H, *J*=2.7 Hz, ArH), 7.25 (dd, 1H, *J*=2.7, 9.3 Hz, ArH), 7.32-7.38 (m, 1H, CH_{vinyl}), 7.51 (d, 2H, *J*=3.7 Hz, ArH), 8.01 (d, 1H, *J*=9.1 Hz, ArH);^{13}C-NMR (62.9 MHz, $CDCl_3$) δ : 30.5 (CH_3), 55.2, 55.6 ($2OCH_3$), 103.0, 112.3, 114.1, 120.5, 121.8, 123.4, 123.6, 124.7, 127.7 (CH), 129.4, 130.1, 130.6, 131.2, 142.4, 144.4, 147.2 (C), 200.3 (CO).

(E)-1-(3-methylquinoxalin-2-yl)-3-(p-tolyl)prop-2-en-1-one (**3d**): M.p. 205 ^{o}C. IR (KBr) [υ, cm^{-1}]: 3074 (C-H)$_{arom}$, 2930, 2865 (C-H)$_{alph}$, 1660 (C=O) , 1570 (C=C); ^{1}H-NMR (300 MHz, $CDCl_3$) δ : 2.19 (s, 3H, CH_3), 2.61 (s, 3H, CH_3), 6.67 (d, 1H, *J* = 15.3 Hz, CH_{vinyl}), 6.97 (d, 2H, *J*=8.0 Hz, ArH), 7.10 (d, 2H, *J*=8.0 Hz, ArH), 7.25-7.29 (m, 2H, ArH), 7.35-7.40 (m, 1H, CH_{vinyl}), 7.55 (d, 1H, *J*=8.1 Hz, ArH), 8.12 (d, 1H, *J*=8.7 Hz, ArH); ^{13}C-NMR (75.5 MHz, $CDCl_3$) δ: 22.1, 30.8 ($2CH_3$), 112.1, 120.9, 122.1, 123.2, 124.2, 125.0, 126.7, 128.3, 129.3, 130.0 (CH), 130.1, 135.5, 135.8, 135.9, 137.5, 159.2 (C), 200.4 (CO).

(E)-1-(3-methylquinoxalin-2-yl)-3-(4-nitrophenyl)prop-2-en-1-one (**3e**): M.p. 215 ^{o}C. IR (KBr) [υ, cm^{-1}]: 3080 (C-H)$_{arom}$, 2935, 2866 (C-H)$_{alph}$, 1660 (C=O), 1575 (C=C), 1550, 1325 (NO_2); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.43 (s, 3H, CH_3), 6.55 (d, 1H, *J*=15.4 Hz, CH_{vinyl}), 6.95 (d, 2H, *J*=8.0 Hz, ArH), 7.07 (d, 2H, *J*=8.0 Hz, ArH), 7.24-7.43 (m, 2H, CH_{vinyl}, ArH), 7.52 (d, 1H, *J*=8.1 Hz, ArH), 7.65 (d, 1H, *J*=8.3 Hz, ArH),8.26 (d, 1H, *J*=8.3 Hz, ArH); ^{13}C-NMR (62.9 MHz, $CDCl_3$) δ: 22.1 (CH_3), 112.1, 120.9, 122.2, 123.3, 124.1, 124.7, 126.3, 126.7, 128.4, 128.6 (CH), 130.1, 130.2, 135.6, 137.5, 138.9, 159.1 (C), 200.3 (CO).

(E)-3-(4-bromophenyl)-1-(3-phenylquinoxalin-2-yl)prop-2-en-1-one (**4a**): M.p. 205 ^{o}C; IR (KBr) [υ, cm^{-1}]: 3086 (C-H)$_{arom}$, 1655 (C=O), 1585 (C=C); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 6.48 (d, 1H, *J*=15.4 Hz, CH_{vinyl}), 6.98 (d, 2H, *J*=8.2 Hz, ArH), 7.08-7.11 (m, 2H, ArH), 7.14 (d, 1H, *J*=8.0 Hz, ArH), 7.24-7.30 (m, 3H, ArH), 7.33-7.36 (m, 1H, CH_{vinyl}), 7.40-7.58 (m, 4H, ArH), 7.62 (dd, 1H, *J*=1.2, 8.0 Hz, ArH); ^{13}C-NMR (75.5 MHz, $CDCl_3$) δ : 113.6, 114.8, 123.8, 123.9, 126.5, 127.1, 127.8, 128.4, 128.5, 129.0, 129.8, 130.9, 131.0, 133.9, 134.0 (CH), 134.3, 135.8, 136.8, 137.2, 140.5, 159.4, 159.6 (C), 200.3 (CO).

(E)-3-(naphthalen-1-yl)-1-(3-phenylquinoxalin-2-yl)prop-2-en-1-one (**4b**): M.p. 235 ^{o}C; IR (KBr) [υ, cm^{-1}]: 3075 (C-H)$_{arom}$, 1655 (C=O), 1575 (C=C); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 6.25 (d, 1H, *J*=15.3 Hz, CH_{vinyl}), 7.06-7.15 (m, 4H, ArH), 7.18-7.21 (m, 2H, ArH), 7.24-7.29 (m, 2H, ArH), 7.30-7.37 (m, 3H, CH_{vinyl} , 2 ArH), 7.42 (d, 2H, *J*=8.2 Hz, ArH), 7.47-7.53 (m, 1H, ArH), 7.58 (dd, 1H, *J*=1.3, 8.2 Hz, ArH), 7.72-7.85 (m, 2H, ArH); ^{13}C-NMR (75.5 MHz, $CDCl_3$) δ : 123.9, 126.5, 126.6, 126.7, 126.8, 127.2, 128.0, 128.3, 128.5, 128.7, 129.0, 129.1, 129.2. 130.1 (CH), 130.2, 130.4 (C), 133.8, 134.3, 134.4, 135.3 (CH), 135.8, 136.7, 136.8, 137.6, 137.7, 139.1 (C), 195.8 (CO).

(E)-3-(3,4-dimethoxyphenyl)-1-(3-phenylquinoxalin-2-yl)prop-2-en-1-one (**4c**): M.p. 206 ^{o}C. IR (KBr) [υ, cm^{-1}]: 3090 (C-H)$_{arom}$, 1655 (C=O), 1580 (C=C); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.82 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 6.31 (d, 1H, *J*=15.4 Hz,

CH_{vinyl}), 6.85-6.86 (m, 1H, ArH), 6.90 (dd, 1H, *J*=1.8, 8.2 Hz, ArH), 7.00 (d, 1H, *J*=8.2 Hz, ArH), 7.04-7.13 (m, 2H, ArH), 7.33-7.38 (m, 1H, CH_{vinyl}), 7.43-7.46 (m, 1H, ArH), 7.50-7.53 (m, 1H, ArH), 7.55-7.60 (m, 2H, ArH), 7.63 (d, 1H, *J*=7.6 Hz, ArH), 7.66 (d, 1H, *J*=9.1 Hz, ArH), 7.69 (dd, 1H, *J*=1.2, 7.8 Hz, ArH); ^{13}C-NMR (62.9 MHz, $CDCl_3$) δ ; 55.8, 55.9 ($2OCH_3$), 113.1, 122.1, 123.8, 126.2, 126.6, 127.2, 128.2, 128.4, 128.5, 128.6, 128.9, 129.3, 129.4 (CH), 133.9, 134.3, 134.4, 134.5 (C), 135.5 (CH), 136.7, 136.9, 140.3, 144.4 (C), 200.3 (CO).

(E)-1-(3-phenylquinoxalin-2-yl)-3-(p-tolyl)prop-2-en-1-one (**4d**): M.p. 225 ^{o}C; IR (KBr) [υ, cm^{-1}]: 3074 $(C-H)_{arom}$, 2935, 2875 $(C-H)_{alph}$, 1665 (C=O), 1575 (C=C); ^{1}H-NMR (300 MHz, $CDCl_3$) δ : 2.40 (s, 3H, CH_3), 6.20 (d, 1H, *J*=15.5 Hz, CH_{vinyl}), 6.85-6.86 (m, 1H, ArH), 6.90 (dd, 1H, *J*=1.8, 8.2 Hz, ArH), 7.00 (d, 1H, *J*=8.2 Hz, ArH), 7.04-7.13 (m, 2H, ArH), 7.26-7.32 (m, 3H, ArH), 7.33-7.38 (m, 1H, CH_{vinyl}), 7.43-7.46 (m, 1H, ArH), 7.50-7.55 (m, 3H, ArH),7.65 (dd, 1H, *J*=1.2, 7.8 Hz, ArH); ^{13}C-NMR (75.5 MHz, $CDCl_3$) δ : 28.8 (CH_3), 113.1, 122.1, 123.8, 126.6, 127.2, 128.3, 128.4, 128.6, 128.8, 129.0, 129.7, 129.8, 129.9 (CH), 134.3, 134.4, 134.8 (C), 135.5, 136.7 (CH), 136.9, 140.4, 144.4, 144.6 (C), 200.3 (CO).

(E)-3-(4-nitrophenyl)-1-(3-phenylquinoxalin-2-yl)prop-2-en-1-one (**4e**): M.p. 206 ^{o}C; IR (KBr) [υ, cm^{-1}]: 3080 $(C-H)_{arom}$, 1666 (C=O), 1575 (C=C), 1555, 1330 (NO_2); ^{1}H-NMR (300 MHz, $CDCl_3$) δ ; 6.29 (d, 1H, *J*=15.2 Hz, CH_{vinyl}), 6.98 (d, 2H, *J*=8.1 Hz, ArH), 7.02 (d, 2H, *J*=8.8 Hz, ArH), 7.08-7.12 (m, 2H, ArH), 7.18 (d, 1H, *J*=8.1 Hz, ArH), 7.22-7.35 (m, 4H, CH_{vinyl}, 3 ArH), 7.42 (d, 1H, *J*=8.2 Hz, ArH), 7.45-7.47 (m, 1H, ArH), 7.62 (d, 1H, *J*=8.3 Hz, ArH); ^{13}C-NMR (75.5 MHz, $CDCl_3$) δ : 116.4, 120.8, 121.9, 124.4, 125.0, 127.1, 127.9, 129.3, 129.6, 129.8, 130.1, 130.2, 130.4, 130.8 (CH), 134.3, 135.0, 135.6 (C), 136.6 (CH), 137.6, 137.7, 140.4, 142.1 (C), 200.3 (CO).

Preparation of 2-(5-(4-bromophenyl)-1-phenyl-4,5-dihydro-1H-pyrazol-3-yl)-3-phenylquinoxaline 5:

Conventional heating method:

A solution of equimolar amounts of chalcone-substituted quinoxaline (**4a**) (1 mmole) and phenyl hydrazine (1 mmole) dissolving in 10 ml glacial acetic acid was refluxed for 4 hrs. After the reaction completed (monitored by TLC), the reaction cooled and neutralized with NH_4OH to produce solid product, filtered and recrystallized with methanol to yield pure product **5**.

Ultrasound-assisted method:

All contents mentioned above were placed in an ultrasonic bath for the period indicated in Table 1, at 50 C^{o} and worked up as described above.

M.p. 245 ^{o}C. IR (KBr) [υ, cm^{-1}]: 3015 $(C-H)_{arom}$, 1601 (C=N), 1585 (C=C), 1228 (C-N); ^{1}H-NMR (300 MHz, $CDCl_3$) δ : 3.21 (d, 2H, *J*= 6.8 Hz, CH_2), 4.61 (t, 1H, *J*=6.6 Hz, $CH_{pyrazol}$), 6.27-6.33 (m, 1H, ArH), 6.95-7.05 (m, 3H, ArH), 7.07-7.12 (m, 3H, ArH), 7.13-7.18 (m, 3H, ArH), 7.20 (d, 1H, *J*=8.1 Hz, ArH), 7.24-7.33 (m, 4H, ArH), 7.42 (td, 1H, *J*= 1.3, 8.2 Hz, ArH), 7.45-7.51 (m, 1H, ArH), 7.57 (d, 1H, *J*=8.2 Hz, ArH); ^{13}C-NMR (75.5 MHz, $CDCl_3$) δ : 57.5 (CH_2), 70.5 ($CH_{pyrazol}$), 123.8, 126.5, 126.6, 126.7, 126.8, 127.2, 128.0, 128.2, 128.5, 128.7, 129.0, 129.1, 129.2, 130.1 (CH), 130.2, 130.4, 133.7 (C), 134.3, 134.4, 135.2, 135.8 (CH), 136.7, 136.8, 137.6, 137.7, 139.1, 140.8 (C).

Preparation of 5-(4-bromophenyl)-3-(3-phenylquinoxalin-2-yl) isoxazole 6:

Conventional heating method:

A mixture of chalcone-substituted quinoxaline (**4a**) (1 mmole), hydroxylamine hydrochloride (1 mmole), and sodium acetate (1 mmole) in 15 ml ethanol was refluxed for 6 hrs until the reaction was completed (the reaction was monitored by TLC). The reaction mixture was concentrated by distilling out the solvent under reduced pressure and poured into ice water. The obtained precipitate was filtered, washed

and recrystallized from a hexane/ethanol mixture to yield a pure product.

Ultrasound-assisted method:

All contents mentioned above were placed in an ultrasonic bath for the period indicated in Table 1, at 50 C^o and worked up as described above.

M.p. 235 ^oC; IR (KBr) [υ, cm^{-1}]:1627 (C=N), 1527 (C=C), 1201 ($C\text{-}O_{isoxazole}$); ^{1}H-NMR (250 MHz, Acetone) δ: 6.60 (s, 1H, $CH_{isoxazole}$), 6.72 (d, 2H, *J*=8.1 Hz, ArH), 6.92-7.12 (m, 5H, ArH), 7.48-7.54 (m, 2H, ArH), 7.62-7.74 (m, 2H, ArH), 7.85 (d, 2H, *J*=8.2 Hz, ArH); ^{13}C-NMR (75.5 MHz, Acetone) δ; 90.4 ($CH_{isoxazole}$), 122.7, 122.9, 123.9, 125.5, 126.2, 126.4, 127.3, 127.4, 128.1 (CH), 128.3, 128.7 (C), 131.7, 132.8, 133.3, 133.5 (CH), 134.1, 135.6, 135.7, 136.5, 137.8, 139.7, 143.5 (C).

Preparation of 6-(4-bromophenyl)-4-(3-phenylquinoxalin-2-yl)-5,6-dihydropyrimidin-2(1*H*)-one 7:

Conventional heating method:

A mixture of chalcone-substituted quinoxaline (**4a**) (1 mmole), urea (1 mmole) and concentrated HCl (0.1 ml) in ethanol (15 ml) was refluxed with stirring on an oil bath at 70-80 C^o for 6 hrs. Subsequently, the reaction mixture was left overnight and then concentrated under reduced pressure to half its volume, and neutralized with ammonium hydroxide. The solid precipitate was filtered off, and purified by column chromatography (flash silica gel, heptane/EtOAc).

Ultrasound-assisted method:

All contents mentioned above were placed in an ultrasonic bath for the period indicated in Table 1, at 60 C^o and worked up, purified as described above.

M.p. 215 ^oC; IR (KBr) [υ, cm^{-1}]: 3251 (N-H), 1665 $(C=O)_{amide}$, 1527 $(C=C)_{arom}$; ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.67 (d, 2H, *J*=8.1 Hz , $CH_{2pyrimidine}$), 4.36 (t, 1H, *J*=7.2 Hz, $CH_{pyrimidine}$), 6.97 (d, 2H, *J*=8.1 Hz, ArH), 7.10 (d, 2H, *J*=8.0 Hz, ArH), (7.22-7.33 (m, 3H, ArH), 7.35-7.42 (m, 2H, ArH), 7.53 (d, 2H, *J*=3.8 Hz, ArH), 8.12 (d, 1H, *J*=8.7 Hz, ArH), 8.30 (d, 1H, *J*=7.8 Hz, ArH), 8.91 (s, 1H, NH); ^{13}C-NMR (75.5 MHz, $CDCl_3$) δ; 40.4 (CH_2), 60.4 ($CH_{pyrimidine}$), 126.5, 127.2, 127.3, 127.4, 128.2, 128.5, 129.1, 129.6, 129.8 (CH), 133.9, 134.3, 134.5, 135.1 (C), 135.8, 136.7, 136.8, 137.5, (CH), 137.6, 138.5, 140.9, 144.5 (C), 192.5 (CO).

Preparation of 1-(5-(4-bromophenyl)-3-(3-phenylquinoxalin-2-yl)-4,5-dihydro-1H-pyrazol-1-yl)ethanone 8:

Conventional heating method:

To the chalcone-substituted quinoxaline **(4a)** (1 mmole) added glacial acetic acid (10 ml) and hydrazine hydrate 99% (1 mmole). The reaction mixture was refluxed for 8 hrs. The resulting solid was filtered, washed with distilled water, and then recrystallized from ethanol.

Ultrasound-assisted method:

All contents mentioned above were placed in an ultrasonic bath for the period indicated in Table 1, at 50 C^o and worked up, purified as described above.

M.p. 240 ^oC. IR (KBr) [υ, cm^{-1}]; 1670 $(C=O)_{acyl}$, 1583 (C=N), 1488 $(C=C)_{arom}$; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.38 (s, 3H, CH_3), 3.75 (d, 2H, *J*= 6.2 Hz, $CH_{2\ pyrazole}$), 4.35 (t, 1H, *J*=67.1 Hz, $CH_{pyrazole}$), 7.06-7.08 (m, 2H, ArH), 7.26-7.30 (m, 1H, ArH), 7.34-7.40 (m, 3H, ArH), 7.42 (dd, 1H, *J*= 1.8, 7.7 Hz, ArH), 7.55 (dd, 1H, *J*= 1.3, 7.7 Hz, ArH), 7.59-7.65 (m, 3H, ArH), 8.02 (d, 2H, *J*=8.1 Hz, ArH). ^{13}C-NMR (75.5 MHz, $CDCl_3$) δ : 30.5 (CH_3), 40.4 (CH_2), 70.4 ($CH_{pyrazol}$), 122.7, 122.9, 123.9, 125.5, 126.2, 126.4, 127.3, 127.4, 128.1 (CH), 128.3, 128.7 (C), 131.7, 132.8, 133.3, 133.5 (CH), 134.1, 135.6, 135.7, 136.5, 137.8, 139.7 (C), 195.6 (CO).

Preparation of 4-(4-bromophenyl)-3-phenyl-6-(3-phenylquinoxalin-2-yl)pyridin-2(3*H*)-one 9:

Conventional heating method:

A mixture of (5 mmole) of phenyl acetamide and (5 mmole) of sodium in 20 ml of dry benzene was heated under reflux for 20 hrs. then (5 mmole) of chalcone-substituted quinoxaline **(4a)** was added and the reaction refluxed for additional 4 h until the reaction was completed (monitored by TLC). The reaction mixture extracted with 50 ml water containing 10% H_2SO_4. The separated aqueous layer was extracted with diethylether and then the organic layer added to a solution of 10% sodium bicarbonate. The combine organic layers (benzene and ether) were dried over anhydrous magnesium sulfate, and concentrated in vacuo. The residue was purified by column chromatography (heptane/EtOAc) to afford compound 9 as a pure product.

Ultrasound-assisted method:

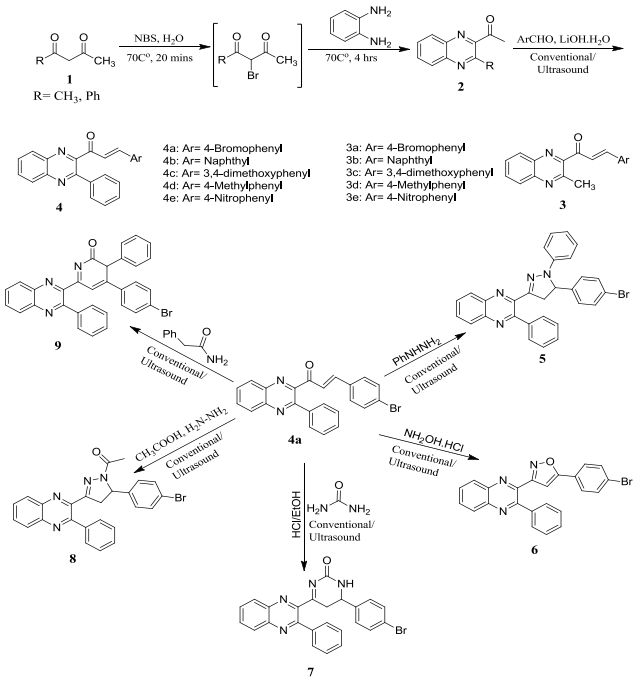
All contents mentioned above were placed in an ultrasonic bath for the period indicated in Table 1, at 60 C^o and worked up, purified as described above.

M.p. 230 ^oC; IR (KBr) [υ, cm^{-1}]: 3095 $(C-H)_{arom}$, 1645 $(C=O)_{amide}$, 1622 (C=N), 1521 $(C=C)_{arom}$. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.92 (s, 1H, $CH_{pyridinone}$), 6.08 (s, 1H, $CH_{pyridinone}$), 6.21-6.27 (m, 1H, ArH), 6.81 (d, 2H, *J*=8.0 Hz, ArH), 6.89 (d, 2H, *J*=8.3 Hz, ArH), 6.93-6.98 (m, 2H, ArH), 7.01-7.08 (m, 2H, ArH), 7.20-7.33 (m, 3H, ArH), 7.36-7.40 (m, 1H, ArH), 7.45 (d, 1H, *J*=8.0 Hz, ArH), 7.48-7.57 (m, 3H, ArH), 7.65 (d, 1H, *J*=8.3 Hz, ArH); ^{13}C-NMR (75.5 MHz, $CDCl_3$) δ: 56.0 ($CH_{pyridinone}$), 110.9, 113.1, 122.1, 123.8, 126.6, 127.2, 128.2, 128.4 (CH), 128.6, 128.8, 129.0, 129.6, 129.7, 134.0 (C), 134.3, 134.4, 134.8, 135.5, 136.7, 136.7, 140.3, 144.4 (CH), 144.5, 148.7 (C), 148.8, 167.4 (CH), 168.2, 168.9 (C), 195.5 (CO).

Results and Discussions

We continue our investigation to obtain functionalized heterocycles compounds through the development of synthetic strategies. The synthesis of the desire compounds was accomplished according to the representation in scheme 1.

The starting material 1-(3-methylquinoxalin-2-yl) ethanone and 1-(phenylquinoxalin-2-yl) ethanone was obtained from reported method by preparation of α-halo-β-keto ester via the reaction of N-bromosuccinimide with phenylene diamine [16].



Scheme 1: Synthesis of quinoxalinyl-chalcones and its derivatives of pyrazoline, isoxazole, pyrimidin-2-one, N-acylpyrazoline and pyridin-2-one moieties.

The present study was achieved the synthesis of chalcone-substituted quinoxalines and other related quinoxaline derivatives by using conventional and ultrasound-assisted methods. Both methods are compared regarding to reaction time, temperature and percentage yields. The chalcone-substituted quinoxalines were prepared by the Claisen-Schmidt condensation of 3-acetylquinoxaline derivative with various aromatic aldehydes in the presence of lithium hydroxide monohydrate ($LiOH.H_2O$) as a catalyst in 1-butanol, as there was no reaction in alcoholic sodium/ potassium hydroxide, and the reaction afforded very low yield when using piperidine as a base (scheme 1). By the use of ultrasound-irradiation method, reaction time was reduced amazingly from 5h

to 60-70 min. for the chalcone-substituted quinoxaline products (**3$_{a-e}$**), (**4$_{a-e}$**) and the yields of reaction products were increased approximately two folds. The same situation was happened for compounds (**5-9**), the time diminished from 4-20 h to 30-90 min. Energetically preparation of chalcone-substituted quinoxalines (**3$_{a-e}$**), (**4$_{a-e}$**) and some of their cyclization derivatives (**5-9**) by using ultrasound assisted method is more adequate than conventional heating method (Table 1). The product yields of chalcone derivatives probably increased due to decrease in cannizzaro reaction [17]. The best temperature for ultrasonic irradiation was found to be 50-60 ^{o}C and the results obtained are given in Table 1.

We found that the ultrasound-assisted results were marvelous compared with conventional heating results. Thus, ultrasonic irradiation was found to have an advantageous effect on the synthesis of chalcone-substituted quinoxalines and the other heterocyclic derivatives compared to traditional method due to low percentage yields, short reaction time, with respect to yield, reaction time, straightforwardness and safeness. The effects of ultrasound were evident in reduction of the processing time; physical processes that create, enlarge, and implode gaseous and vaporous cavities in an irradiated liquid. The cavitations induce very high local temperatures and pressures inside the bubbles (cavities), hence enhancing the mass transfer and allowing chemical reactions to occur quickly [18] [19]. To the best of our knowledge, this method provides the first example of an efficient ultrasound-promoted approach for the synthesis of chalcone-substituted quinoxalines and their cyclization derivatives containing moieties of pyrazoline, isoxazole, pyrimidin-2-one, *N*-acylpyrazoline and pyridin-2-one. This strategy is the simplest and compatible would be viable for the synthesis of various types of other nitrogen-containing heterocyclic compounds.

The structures of all the synthesized compounds have been confirmed by their spectroscopic data, such as ^{1}H-NMR, ^{13}C-NMR, and FT-IR. It is noteworthy to point out that in ^{1}H-NMR spectra of the described chalcone-substituted quinoxalines, α, β-unsaturated enone system protons have appeared as two doublets between δ 6.0 ppm and 7.5 ppm for H_β and H_α respectively, the values of coupling approximately were around 15Hz probably predict that chalcones derivatives are trans isomers [24].

Table 1: Prepared chalcone-substituted quinoxalines (3_{a-e}), (4_{a-e}) and some of related cyclic derivatives (5-9) under different heating methods.

Comp.	Conventional time (h) of reflux	Yield (%)	Ultrasound-assisted time (min.) at 50-60 ^{o}C	Yield (%)
3a	5	45	60	75
3b	5	40	75	77
3c	5	50	70	85
3d	5	55	70	88
3e	5	35	75	70
4a	5	50	60	80
4b	5	45	70	80
4c	5	50	70	85
4d	5	48	74	85
4e	5	40	72	80
5	4	32	90	68
6	6	30	85	65
7	6	30	30	63
8	8	36	80	75
9	20	40	90	75

In all the chalcone derivatives, the signal of the second enone proton not easily recognized due to multiplet signals of aromatic protons. The other peaks in the spectra have appeared in the expected region and the numbers of protons belong to compound structure are in accordance with the expected protons. Additional support to clarify the chalcone-substituted quinoxalines (**3$_{a-e}$**), (**4$_{a-e}$**) structures was obtained from ^{13}C-NMR and FT-IR spectrum. The appearance of peak around 200 ppm indicates the carbon of α, β-unsaturated

carbonyl of chalcone. The FT-IR spectrum of compounds (**3_{a-e}**), (**4_{a-e}**) shows an absorption band around 1660cm^{-1} and 1570 cm^{-1} due to C=O and C=C of α, β-unsaturated enone respectively, and also a band above 3000 cm^{-1} due to aromatic (C-H). The synthesis of quinoxaline derivative with pyrazoline ring (**5**), by reaction of quinoxalinyl-chalcone **4a** with phenyl hydrazine was achieved by conventional heating and ultrasonic irradiation method. The ^{1}H-NMR spectrum of compound **5** exhibited a doublet and triplet signals at 3.21 and 4.61 ppm belongs to 2H and 1H in pyrazoline ring, with the disappearance of two doublets of H_{β} and H_{α} for α, β-unsaturated enone as depicted by Figure 1, while the total number of carbon atoms illustrated by Figure 2. The FT-IR spectrum showed a new absorption band at 1601 cm^{-1} due to stretching vibration of C=N, with disappearance of the carbonyl group band in α, β-unsaturated enone.

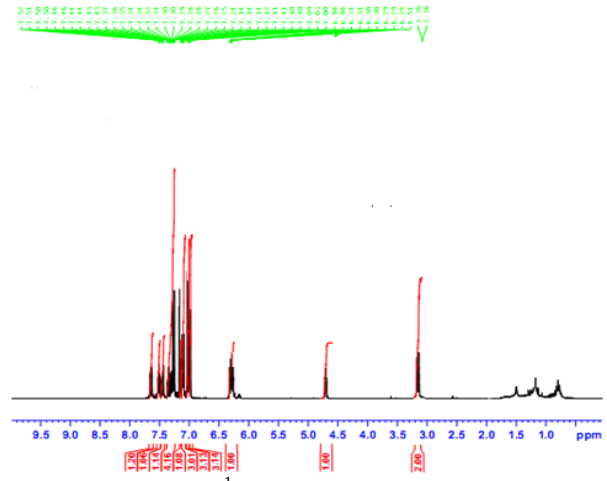


Figure 1. ^{1}H-NMR of compound 5.

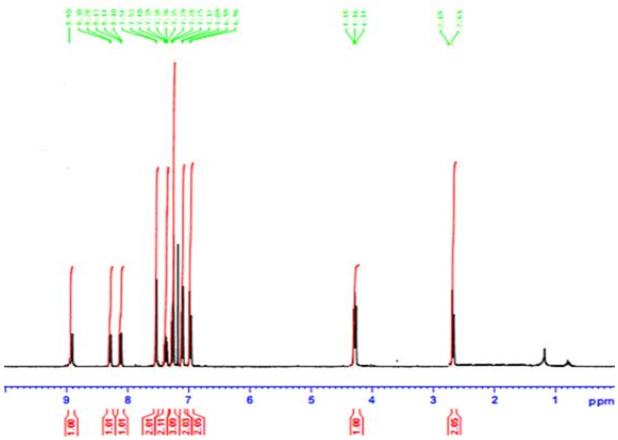


Figure 2: ^{13}C-NMR of compound 5.

Quinoxaline derivative containing isoxazole moiety (**6**) was synthesized by the reaction of compound **4a** with hydroxyl amine under traditional heating and ultrasound-assisted method. The FT-IR spectrum of compound **6** showed band at 1627 cm^{-1} belong the stretching vibration of C=N in the isoxazole ring with absence of C=O vibration in α, β-unsaturated enone at 1655 cm^{-1}. The ^{1}H-NMR spectrum also confirms the structure by appearing singlet peak at 6.60 ppm of one proton in isoxazole ring.

Reaction of quinoxalinyl-chalcone 4a with urea in acidic medium under conventional heating and ultrasonic irradiation afforded quinoxaline derivative with pyrimidin-2-one moiety (**7**). The ^{1}H-NMR spectrum of this compound (Figure 3) showed doublet signal of two protons at 2.67 ppm and triplet signal of one proton at 4.36 ppm both belong to pyrimidine ring.

The FT-IR exhibited a new band at 3251 cm^{-1} indicate the presence of N-H bond and a band at 1665 cm^{-1} due to C=O group of amide. The structure of compound 7 strongly confirmed by the ^{13}C-NMR analysis as shown in Figure 4.

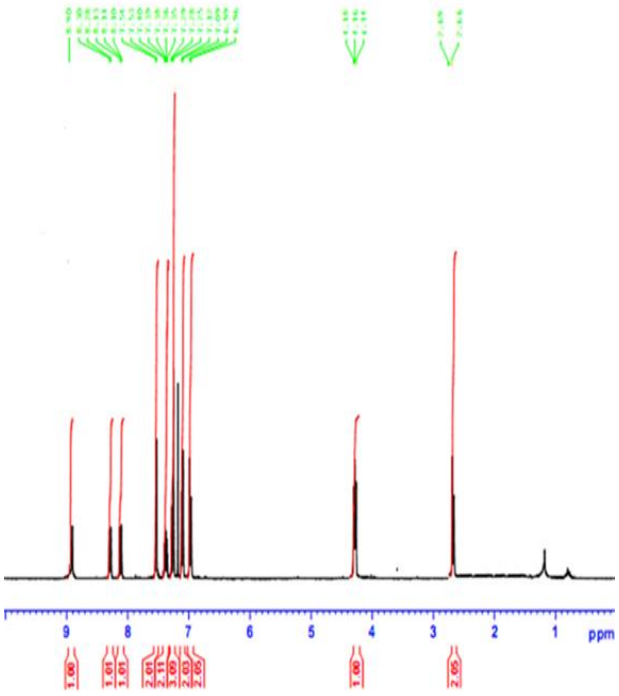


Figure 3: ^{1}HNMR of Compound 7.

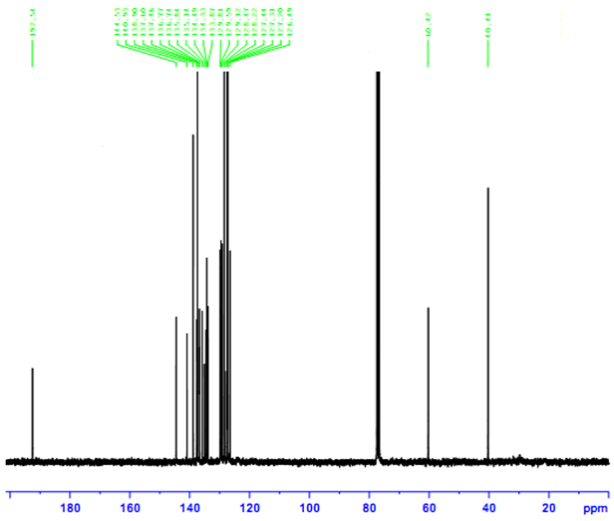


Figure 4: ^{13}C-NMR of Compound 7.

Quinoxaline compound 8 was synthesized by reaction of quinoxalinyl chalcone **4a** with hydrazine hydrate in the presence of acetic acid under conventional heating and ultrasound assisted methods. The structure elucidated by IR, ^{1}HNMR and ^{13}CNMR (see the experimental section). Quinoxaline derivative bearing pyridine-2-one ring (**9**) was synthesized by reaction of quinoxalinyl chalcone **4a** with phenyl acetamide also under conventional heating and ultrasound assisted methods. The ^{1}H-NMR spectrum of compound **9** showed two singlets at 3.29 ppm and 6.08 ppm of two protons in pyridine ring, the aromatic protons are observed between 6.21 and 7.65 ppm. The FT-IR spectrum demonstrated a new band at 1622 cm^{-1} indicated the presence of the C=N group and another band at 1645 cm^{-1} represented the stretching vibration of amide carbonyl (C=O).

Conclusions

This article reported the synthesis of 10 chalcone-substituted quinoxaline derivativos and 5 novel quinoxaline derivatives containing of pyrazoline, isoxazole, pyrimidin-2-one, *N*-acylpyrazoline and pyridin-2-one moieties under conventional heating conditions and ultrasound conditions. We conclude that the sonochemical reactions are simple to execute and the products are isolated in good yields with short reaction time when compared to the conventional conditions of synthesis.

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