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Short Communication

Benign methodology and improved synthesis of 5-(2-chloroquinolin-3-yl)-3-phenyl-4,5-dihydroisoxazoline using acetic acid aqueous solution under ultrasound irradiation

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ABSTRACT

In the present paper, we have executed the synthesis of substituted 5-(2-chloroquinolin-3-yl)-3-phenyl-4,5-dihydroisoxazolines via the reactions of substituted 3-(2-chloroquinolin-3-yl)-1-phenylprop-2-en-1-ones with hydroxylamine hydrochloride and sodium acetate in aqueous acetic acid solution in 72–90% yields at room temperature under ultrasound irradiation. This method provides several advantages such as operational simplicity, higher yield, safety and environment friendly protocol. The resulting substituted isoxazolines were characterized on the basis of ^{1}H NMR, ^{13}C NMR, IR, elemental analysis, and mass spectral data.

1. Introduction

In the recent years, organic reactions driven in aqueous media have attracted increasing interest currently because of environmental issues and the understanding of biochemical processes. As a reaction solvent, water offers many practical and economic advantages including low cost, safe handling and environmental compatibility. Many organic reactions in aqueous media have been described in the literature [1]. In the recent years, organic reactions carried out in aqueous media have received much attention from chemists [2] because of concerns and compatibility about the environment [3]. Also, most organic reactants including catalysts are insoluble in water, and the surfactants, due to their hydrophobic and hydrophilic nature, form micelles of the reactants and promote the reaction to occur in water [4].

Ultrasound has increasingly been used in organic synthesis in the last three decades. Ultrasonic irradiation leads to the acceleration of numerous catalytic reactions in homogeneous and heterogeneous systems [5]. Furthermore, significant improvements can be realized with respect to the yields [6,7]. The ultrasonic sonochemical phenomenon originates from the interaction between a suitable field of acoustic waves and a potentially reacting chemical system. The interaction takes place through the intermediate phenomenon of acoustic cavitations. Three important factors have to be considered when an ultrasonic induced reaction is performed: the acoustic field, the bubbles field and the chemical system [8,9]. The chemical effects of ultrasounds have been attributed to implosive collapse of the cavitations period of the sound waves. The bubbles are generated at localized sites in the liquid mixture that contain small amounts of dissolved gases. Trapped within a micro bubble, the reactants are exposed to a high pressure and temperature upon implosion and the molecules are fractured forming highly reactive species with a great tendency to react with the surrounding molecules. When one of the phases is a solid, the ultrasonic irradiation has several additional enhancement effects, and this is especially useful when the solid acts as a catalyst [10]. The cavitation effect form microjects of solvent which bombard the solid surface. This fact causes the exposition of unreacted surfaces of solid and increases the chances of interphase surface able to react. In general, the sonications have beneficial effects on the chemical reactivity, such as to accelerate the reaction, to reduce the induction period and to enhance the efficiency of the catalyst.

The isoxazoline nucleus is well known for its medicinal importance [11] and a number of related compounds are known to exhibit antitumor [12] properties. Diaryl isoxazole derivatives have a wide range of biological properties and commercial application in various realm of therapy, including cytotoxic [13] agents. Isoxazoline also serves as anti-influenza viral activity [14], inhibition of human leukocyte elastase and cathepsin G [15]. The marketed drugs of isoxazole, such as, acetylsulfisoxazole, cycloserine, drazoxol, Sulfisoxazole and zonisamide have a great medicinal

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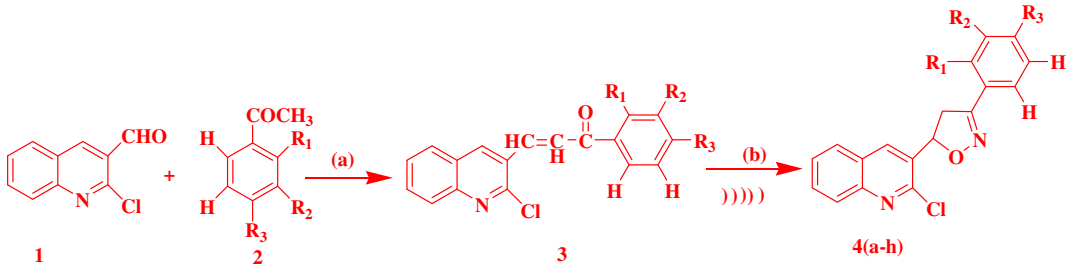


	R1	R2	R3
4a	-H	-H	-H
4b	-Cl	-H	-Cl
4c	-H	-Cl	-Cl
4d	-H	-H	$-CH_3$
4e	$-CH_3$	-H	-H
4f	-H	-H	$-OCH_3$
4g	-H	-H	-Br
4h	-H	$-NO_2$	-H

Where: a) MeOH, 20% NaOH, stir, 24 h. b) $NH_2OH.HCl$, CH_3COOH , CH_3COONa , H_2O ,under ultrasonicator.

Scheme 1. Synthesis of target molecule **4**(**a**–**h**).

value. These drugs show antimicrobial [16,18], tuberculostatic [19], anticonvulsant [20], neurotoxic [21] and antiepileptic activities [22] and these activities are also observed in their derivatives which led to the search for newer bioactive compounds of this class.

A variety of methods have been reported for the preparation of this class of compounds. Gurubasavaraja Swamy et al. have synthesized isoxazoline bearing hydroxy benzofuran from chalcones and hydroxyl amine hydrochloride in presence of fused anhydrous sodium acetate by refluxing for 7 h [23]. Vikas Desai reported the reaction of substituted chalcones and hydroxylamine hydrochloride in presence of potassium hydroxide in absolute ethanol [24]. Marei et al. reported the synthesis of 5-hydroxy-2-isoxazolines from acetylenic ketone and hydroxyl amine hydrochloride in sodium acetate by refluxing for 5–8 h [25]. These reaction conditions suffer from economic and environmental concerns. Recently, NaOH and K_2CO_3-mediated microwave irradiation has been shown to be an efficient method for the synthesis of isoxazolines [26]. Keeping in view, the advantages of ultrasonic irradiation, we wish to report an efficient and practical procedure for the synthesis of substituted 5-(2-chloroquinolin-3-yl)-3-phenyl-4,5-dihydroisoxazolines with chalcones and hydroxylamine hydrochloride in sodium acetate–acetic acid aqueous solution under ultrasound irradiation (Scheme 1).

2. Experimental

2.1. Chemicals and apparatus

All the reagents, solvents and catalyst are of analytical grade purchased from a commercial source and used directly. All the melting points were determined by open tube capillaries method and are uncorrected. The purity of compounds was checked routinely by TLC (0.5 mm thickness) using silica gel-G coated Al-plates (Merck) and spots were visualized by exposing the dry plates in iodine vapours. IR spectra (ν_{max} in cm^{-1}) were recorded on a Schimadzu-IR Prestige 21 spectrophotometer using KBr technique; ^1H NMR spectra and ^{13}C NMR spectra of the synthesized compounds were recorded on a Bruker-Avance II 400 (400 MHz), Varian-Gemini (200 MHz) spectrophotometer using DMSO-d_6 solvent and TMS as the internal standard. Mass spectra were recorded on a Micromass Q-ToF high resolution mass spectrometer equipped with electrospray ionization (ESI) on Masslynx 4.0 data acquisition system. The elemental analysis (C, H, N, and S) of compounds was performed on Carlo Erba-1108 elemental analyzer. The results were found to be in good agreement with the calculated values. The ultrasonic assisted reactions are carried out in a "Spectralab model UCB 40D Ultrsonic cleaner" with a frequency of 40 kHz and a nominal power 250 W. The reaction flask was located in the cleaner, where the surface of reactants is slightly lower than the level of the water. The reaction temperature was controlled by addition or removal of water from ultrasonic bath.

2.2. Synthesis of 3-(2-chloroquinolin-3-yl)-1-substituted phenyl prop-2-en-1-ones

To the solution of (0.01 mol) 2-chloroquinoline-3-carbaldehyde in 5 ml of methanol, freshly prepared 2 N methanolic NaOH solutions (30 ml) was added in ice cold condition and stirred for 10 min. To this (0.01 mol) of appropriate ketones was added and the reaction mixture was stirred at room temperature for 24 h. 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.

2.2.1. 3-(2-Chloroquinolin-3-yl)-1-phenylprop-2-en-1-one (**3a**)

Yield: 74%; R_f = 0.44 in EtOAc/hexane, 3:7; yellow solid. m.p.: 132–140 °C; MS (M^+): 293.75 (100%), 295.07 (33%). FTIR (cm^{-1}): 1662 (C=O), 1619 (CH=CH), 853 (C—Cl); ^1H NMR (400 MHz, DMSO d_6): δ/ppm 7.53 (1H, d, J = 15.4 Hz, H_α), 8.52 (1H, d, J = 15.5 Hz, H_β),

7.40–8.31 (m, 1H, 2H, 3H, 4H, 5H, 1′H, 2′H, 3′H, 4′H, 5′H); ^{13}C NMR (200 MHz, DMSO-d_6): δ 128.4 (C_α), 146.5 (C_β), 187.4 (>C═O), 149.6 (C1-quinoline), 130.6 (C2-quinoline), 135.8 (C3-quinoline), 129.2 (C4-quinoline), 127.6 (C5-quinoline), 130.4 (C6-quinoline), 127.7 (C7-quinoline), 126.9 (C8-quinoline), 148.3 (C9-quinoline), 138.8 (C1-Phenyl), 128.4 (C2-Phenyl), 130.8 (C3-Phenyl), 134.8 (C4-Phenyl), 129.6 (C5-Phenyl), 128.8 (C6-Phenyl). 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.

*2.2.2. 3-(2-Chloroquinolin-3-yl)-1-(2,4-dichorophenyl-) prop-2-en-1-one (**3b**)*

Yield: 77%, R_f = 0.65 in EtOAc/hexane, 3:7. Pale yellow solid. m.p.: 135–138 °C; MS (M^+): 360.68 (100%), 362.73 (95%). FTIR (cm^{-1}): 1664 (C═O), 1614 (CH═CH), 852 (C—Cl); ^{1}H NMR (400 MHz, DMSO d_6) δ/ppm: 7.65 (1H, d, J = 15.2 Hz, H_α), 8.51 (1H, d, J = 15.6 Hz, H_β), 7.34–8.32 (m, 1H, 2H, 3H, 4H, 5H, 2′H, 4′H, 5′H). ^{13}C NMR (200 MHz, DMSO-d_6): δ 128.5 (C_α), 145.6 (C_β), 189.4 (>C═O), 149.4 (C1-quinoline), 130.3 (C2-quinoline), 135.7 (C3-quinoline), 129.1 (C4-quinoline), 127.8 (C5-quinoline), 130.4 (C6-quinoline), 127.9 (C7-quinoline), 126.6 (C8-quinoline), 148.4 (C0-quinoline), 136.2 (C1-Phenyl), 136.4 (C2-Phenyl), 130.9 (C3-Phenyl), 141.5 (C4-Phenyl), 127.6 (C5-Phenyl), 132.8 (C6-Phenyl); 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.

*2.2.3. 3-(2-Chloroquinolin-3-yl)-1-(3,4-dichlorophenyl)prop-2-en-1-one (**3c**)*

Yield: 73%, R_f = 0.61 in EtOAc/hexane, 3:7. Pale yellow solid. m.p.: 145–148 °C; MS (M^+): 360.47 (100%), 362.73 (96%). FTIR (cm^{-1}): 1660 (C═O), 1613 (CH═CH), 855 (C—Cl); ^{1}H NMR (400 MHz, DMSO d_6): δ/ppm 7.34 (1H, d, J = 15.5 Hz, H_α), 8.55 (1H, d, J = 15.7 Hz, H_β), 7.54–8.25 (m, 1H, 2H, 3H, 4H, 5H, 1′H, 4′H, 5′H). ^{13}C NMR (200 MHz, DMSO-d_6): δ 128.1 (C_α), 145.3 (C_β), 189.3 (>C═O) 149.1 (C1-quinoline), 130.3 (C2-quinoline), 135.5 (C3-quinoline), 129.7 (C4-quinoline), 127.2 (C5-quinoline), 130.4 (C6-quinoline), 127.6 (C7-quinoline), 126.8 (C8-quinoline), 148.4 (C9-quinoline), 138.2 (C1-Phenyl), 131.4 (C2-Phenyl), 134.9 (C3-Phenyl), 140.3 (C4-Phenyl), 130.1 (C5-Phenyl), 128.2 (C6-Phenyl); 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.

*2.2.4. 3-(2-Chloroquinolin-3-yl)-1-p-tolyl prop-2-en-1-one (**3d**)*

Yield: 75%, R_f = 0.56 in EtOAc/hexane, 3:7. Yellow crystalline solid. m.p.: 140–148 °C; ESI-MS (M^+): 307.10 (100%), 309.07 (32%). FTIR (cm^{-1}): 1668 (C═O), 1616 (CH═CH), 851 (C—Cl); ^{1}H NMR (400 MHz, DMSO d_6): δ/ppm 2.38 (3H, s, CH_3), 7.54 (1H, d, J = 15.4 Hz, H_α), 8.59 (1H, d, J = 15.6 Hz, H_β), 7.29–8.33 (m, 1H, 2H, 3H, 4H, 5H, 1′H, 2′H, 4′H, 5′H). ^{13}C NMR (200 MHz, DMSO-d_6): δ 129.1 (C_α), 146.2 (C_β), 188.3 (>C═O), 22.7 (–CH_3), 149.5 (C1-quinoline), 130.3 (C2-quinoline), 135.1 (C3-quinoline), 129.7 (C4-quinoline), 127.2 (C5-quinoline), 130.8 (C6-quinoline), 127.4 (C7-quinoline), 126.6 (C8-quinoline), 148.3 (C9-quinoline), 134.9 (C1-Phenyl), 130.8 (C2-Phenyl), 129.9 (C3-Phenyl), 144.5 (C4-Phenyl), 129.8 (C5-Phenyl), 130.3 (C6-Phenyl). 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.

*2.2.5. 3-(2-Chloroquinolin-3-yl)-1-o-tolyl prop-2-en-1-one (**3e**)*

Yield: 78%, R_f = 0.51 in EtOAc /hexane, 3:7. Yellow crystalline solid. m.p.: 132–140 °C; ESI-MS (M^+): 307.12 (100%), 309.10 (35%). FTIR(cm^{-1}):1663 (C═O), 1615 (CH═CH), 854 (C–Cl); ^{1}H NMR (400 MHz, DMSO d_6): δ/ppm 2.38 (3H, s, CH_3), 7.54 (1H, d, J = 15.6 Hz, H_α), 8.51 (1H, d, J = 15.7 Hz, H_β), 7.29–8.27 (m, 1H, 2H, 3H, 4H, 5H, 2′H, 3′H, 4′H, 5′H). ^{13}C NMR (200 MHz, DMSO-d_6): δ 129.3 (C_α), 146.5 (C_β), 188.6 (>C═O), 18.6 (–CH_3), 149.2 (C1-quinoline), 130.6 (C2-quinoline), 135.1 (C3-quinoline), 129.5 (C4-quinoline), 127.6 (C5-quinoline), 130.1 (C6-quinoline), 127.0 (C7-quinoline), 126.1 (C8-quinoline), 148.5 (C9-quinoline), 133.8 (C1-Phenyl), 139.6 (C2-Phenyl), 132.4 (C3-Phenyl), 134.5 (C4-Phenyl), 126.4 (C5-Phenyl), 128.5 (C6-Phenyl). 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.

*2.2.6. 3-(2-Chloroquinolin-3-yl)-1-(4-methoxyphenyl) prop-2-en-1-one (**3f**)*

Yield: 74%; R_f = 0.59 in EtOAc/hexane, 3:7. Pale yellow crystalline solid. m.p.: 146–150 °C; ESI-MS (M^+): 323.13 (100%), 325.57 (37%). FTIR (cm^{-1}): 1667 (C═O), 1618 (CH═CH), 2827 (–OCH_3), 853 (C–Cl). ^{1}H NMR (400 MHz, DMSO d_6): δ/ppm 7.54 (1H, d, J = 15.3 Hz, H_α), 8.53 (1H, d, J = 15.6 Hz, H_β), 7.43–8.31 (m, 1H, 2H, 3H, 4H, 5H, 1′H, 2′H, 4′H, 5′H). ^{13}C NMR (200 MHz, DMSO-d_6): δ 129.1 (C_α), 146.2 (C_β), 187.9 (>C═O), 55.7 (–OCH_3), 149.3 (C1-quinoline), 130.1 (C2-quinoline), 135.5 (C3-quinoline), 129.0 (C4-quinoline), 127.7 (C5-quinoline), 130.9 (C6-quinoline), 127.3 (C7-quinoline), 126.8 (C8-quinoline), 148.1 (C9-quinoline), 130.2 (C1-Phenyl), 131.9 (C2-Phenyl), 114.8 (C3-Phenyl), 166.5 (C4-Phenyl), 115.3 (C5-Phenyl), 130.9 (C6-Phenyl). Anal. Calcd: $C_{19}H_{14}ClNO_2$: C, 70.46; H, 4.39; N, 4.38. Found: C, 70.49; H, 4.42; N, 4.38.

*2.2.7. 3-(2-Chloroquinolin-3-yl)-1-(4-bromophenyl) prop-2-en-1-one (**3g**)*

Yield: 76%, R_f = 0.58 in EtOAc/hexane, 3:7. Yellow crystalline solid. m.p.: 166–170 °C; ESI-MS (M^+): 372.12 (100%), 370.67 (77%). FTIR (cm^{-1}): 1664 (C═O), 1613 (CH═CH), 853 (C–Cl), 588 (C–Br); ^{1}H NMR (400 MHz, DMSO d_6): δ/ppm 7.54 (1H, d, J = 15.5 Hz, H_α), 7.90 (1H, d, J = 15.7 Hz, H_β), 7.43–8.32 (m, 1H, 2H, 3H, 4H, 5H, 1′H, 2′H, 4′H, 5′H). ^{13}C NMR (200 MHz, DMSO-d_6): δ 129.5 (C_α), 146.2 (C_β), 187.3 (>C═O), 149.5 (C1-quinoline), 130.1 (C2-quinoline), 135.9 (C3-quinoline), 129.2 (C4-quinoline), 127.9 (C5-quinoline), 130.6 (C6-quinoline), 127.1 (C7-quinoline), 126.2 (C8-quinoline), 148.9 (C9-quinoline), 136.9 (C1-Phenyl), 132.1 (C2-Phenyl), 134.5 (C3-Phenyl), 128.5 (C4-Phenyl), 132.1 (C5-Phenyl), 132.8 (C6-Phenyl). 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.

*2.2.8. 3-(2-Chlroquinolin-3-yl)-1-(3-nitrophenyl) prop-2-en-1-one (**3h**)*

Yield: 70%, R_f = 0.54 in EtOAc/hexane, 4:6. Pale yellow solid. m.p.: 145–150 °C; ESI-MS (M^+): 338.09 (100%), 340.06 (32%). FTIR (cm^{-1}): 1662 (C═O), 1615 (CH═CH), 855 (C–Cl), 1589 (–NO_2); ^{1}H NMR (400 MHz, DMSO d_6): δ/ppm 7.53 (1H, d, J = 15.6 Hz, H_α), 8.51 (1H, d, J = 15.7 Hz, H_β), 7.43–8.10 (m, 1H, 2H, 3H, 4H, 5H, 1′H, 3′H, 4′H, 5′H). ^{13}C NMR (200 MHz, DMSO-d_6): δ 129.5 (C_α), 146.1 (C_β), 187.7 (>C═O), 149.7 (C1-quinoline), 130.5 (C2-quinoline), 135.4 (C3-quinoline), 129.6 (C4-quinoline), 127.2 (C5-quinoline), 130.1 (C6-quinoline), 127.3 (C7-quinoline), 126.9 (C8-quinoline), 148.3 (C9-quinoline), 138.9 (C1-Phenyl), 124.1 (C2-Phenyl), 148.2 (C3-Phenyl), 126.6 (C4-Phenyl), 130.1 (C5-Phenyl), 136.0 (C6-Phenyl). 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.

2.3. Ultrasonic mediated aqueous acetic acid catalyzed general synthesis of 5-(2-chloroquinolin-3-yl)-3-substituted phenyl-4,5-dihydroisoxazoline

The reaction was carried out in Spectralab model UCB 40D Ultrasonic cleaner. Chalcones (**3**, 2 mmol), hydroxylamine hydrochloride (6 mmol) and sodium acetate (0.3 mmol) were dissolved in acetic acid aqueous solution (8 mL, HAc/H_2O = 2/1, V/V) in a 50 ml conical flask. The mixture was irradiated in the water bath

Table 1
Time taken and % yield for compounds **4**(**a**–**h**).

Compound	Conventional method		Ultrasonic method					
			1:1 mol ratio		1:2 mol ratio		1:3 mol ratio	
	Time (h)	% Yield	Time (h)	% Yield	Time (h)	% Yield	Time (h)	% Yield
4a	6	76	1.5	80	1.5	85	1.5	89
4b	7	74	2	82	2	84	2	87
4c	6	77	2	81	2	83	2	89
4d	6.5	78	2	80	2	86	2	90
4e	6	72	2	82	2	85	2	87
4f	7	73	2	80	2	83	2	87
4g	7	75	2	81	2	84	2	88
4h	6	74	2	80	2	86	2	89

of an ultrasonic cleaner for the period as indicated in Table 1. The progress of the reaction was monitored by TLC. The reaction mixture was poured into crushed ice. The precipitate was separated by filtration, washed with water, and recrystallized from ethanol to obtain the 5-(2-chloroquinolin-3-yl)-3-phenyl-4,5-dihydroisoxazolines 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.

*2.3.1. 5-(2-Chloroquinolin-3-yl)-3-phenyl-4,5-dihydroisoxazoline (**4a**)*

R_f = 0.64 in EtOAc/hexane, 4:6. Brown crystalline solid. m.p.: 141–145 °C; ESI-MS (M^+): 308.09 (100%), 310.06 (36%). FTIR (cm^{-1}): 1635 (C═N, quinoline), 1637(C═N, isoxazoline), 1231 (–C–O–N), 823 (C–Cl). ^{1}H NMR (400 MHz, DMSO d_6): δ/ppm 5.93 (1H, t, J = 9.8 Hz, –C–CH–O–), 3.97 (2H, d, J = 9.4 Hz, –C–CH_2–C–), 7.43–8.27 (m, 1H, 2H, 3H, 4H, 5H, 1′H, 2′H, 3′H, 4′H, 5′H). ^{13}C NMR (200 MHz, DMSO-d_6): δ 156.3 (C1-Isoxazoline), 43.9 (C2-Isoxazoline), 72.9 (C3-Isoxazoline), 150.3 (C1-quinoline), 131.4 (C2-quinoline), 136.2 (C3-quinoline), 127.2 (C4-quinoline), 128.0 (C5-quinoline), 130.9 (C6-quinoline), 126.3 (C7-quinoline), 128.2 (C8-quinoline), 145.1 (C9-quinoline), 134.2 (C1-Phenyl), 130.9 (C2-Phenyl), 128.8 (C3-Phenyl), 131.5 (C4-Phenyl), 129.3 (C5-Phenyl), 130.2 (C6-Phenyl). Anal. Calcd: $C_{18}H_{13}ClN_2O$: C, 70.71; H, 4.26; N, 9.24. Found: C, 70.84; H, 4.28; N, 9.28.

*2.3.2. 5-(2-Chloroquinolin-3-yl)-3-(2,4-dichlorophenyl)-4,5-dihydroisoxazoline (**4b**)*

R_f = 0.53 in EtOAc/hexane, 3:7. Yellowish brown solid. m.p.: 149–151 °C; ESI-MS (M^+): 375.75 (100%), 377.16 (76%). FTIR (cm^{-1}): 1633 (C═N, quinoline), 1636 (C═N, isoxazoline), 1231 (–C–O–N), 825 (C–Cl); ^{1}H NMR (400 MHz, DMSO d_6): δ/ppm 5.91 (1H, t, J = 9.7 Hz –C–CH–O–), 3.98 (2H, d, J = 9.2 Hz –C–CH_2–C–), 7.47–8.16 (m, 1H, 2H, 3H, 4H, 5H, 3′H, 5′H). ^{13}C NMR (200 MHz, DMSO-d_6): δ 156.2 (C1-Isoxazoline), 43.5 (C2-Isoxazoline), 72.7 (C3-Isoxazoline), 150.2 (C1-quinoline), 131.0 (C2-quinoline), 136.3 (C3-quinoline), 127.1 (C4-quinoline), 128.8 (C5-quinoline), 130.3 (C6-quinoline), 126.5 (C7-quinoline), 128.6 (C8-quinoline), 145.3 (C9-quinoline), 135.3 (C1-Phenyl), 134.9 (C2-Phenyl), 130.5 (C3-Phenyl), 138.0 (C4-Phenyl), 127.1 (C5-Phenyl), 132.2 (C6-Phenyl). Anal. Calcd: $C_{18}H_{11}Cl_3N_2O$: C, 57.21; H, 2.86; N, 7.34. Found: C, 57.24; H, 2.88; N, 7.38.

*2.3.3. 5-(2-Chloroquinolin-3-yl)-3-(3,4-dichlorophenyl)-4,5-dihydroisoxazoline (**4c**)*

R_f = 0.58 in EtOAc/hexane, 3:7. Light brown solid. m.p.: 158–160 °C; ESI-MS (M^+): 375.45 (100%), 377.12 (71%). FTIR (cm^{-1}): 1638 (C═N, quinoline), 1632 (C═N, isoxazoline), 1236 (–C–O–N), 827 (C–Cl); ^{1}H NMR (400 MHz, DMSO d_6): δ/ppm 5.95 (1H, t, J = 9.8 Hz, –C–CH–O–), 3.96 (2H, d, J = 9.4 Hz, –C–CH_2–C–), 7.47–8.16 (m, 1H, 2H, 3H, 4H, 5H, 4′H, 5′H). ^{13}C NMR (200 MHz, DMSO-d_6): δ 156.1 (C1-Isoxazoline), 43.8 (C2-Isoxazoline), 72.5 (C3-Isoxazoline), 150.2 (C1-quinoline), 131.4 (C2-quinoline), 136.6 (C3-quinoline), 127.8 (C4-quinoline), 128.1 (C5-quinoline), 130.3 (C6-quinoline), 126.5 (C7-quinoline), 128.7 (C8-quinoline), 145.9 (C9-quinoline), 133.5 (C1-Phenyl), 130.7 (C2-Phenyl), 133.5 (C3-Phenyl), 135.7 (C4-Phenyl), 130.4 (C5-Phenyl), 128.7 (C6-Phenyl). Anal. Calcd: $C_{18}H_{11}Cl_3N_2O$: C, 57.25; H, 2.85; N, 7.37. Found: C, 57.22; H, 2.86; N, 7.39.

*2.3.4. 5-(2-Chloroquinolin-3-yl)-3-p-tolyl-4,5-dihydroisoxazoline (**4d**)*

R_f = 0.63 in EtOAc/hexane, 3:7. Dark brown crystalline solid. m.p.: 162–165 °C; ESI-MS (M^+): 322.07 (100%), 324.16 (37%). FTIR (cm^{-1}): 1634 (C═N, quinoline), 1633 (C═N, isoxazoline), 1235 (–C–O–N), 823 (C–Cl); ^{1}H NMR (400 MHz, DMSO d_6): δ/ppm 2.43 (3H, s, CH_3), 5.93 (1H, t, J = 9.8 Hz, –C–CH–O–), 3.99 (2H, d, J = 9.5 Hz, –C–CH_2–C–), 7.37–8.16 (m, 1H, 2H, 3H, 4H, 5H, 1′H, 2′H, 4′H, 5′H). ^{13}C NMR (200 MHz, DMSO-d_6): δ 156.4 (C1-Isoxazoline), 43.6 (C2-Isoxazoline), 72.8 (C3-Isoxazoline), 25.7 (–CH_3), 150.2 (C1-quinoline), 131.5 (C2-quinoline), 136.8 (C3-quinoline), 127.3 (C4-quinoline), 128.6 (C5-quinoline), 130.5 (C6-quinoline), 126.8 (C7-quinoline), 128.9 (C8-quinoline), 145.1 (C9-quinoline), 132.0 (C1-Phenyl), 129.1 (C2-Phenyl), 129.8 (C3-Phenyl), 142.7 (C4-Phenyl), 129.2 (C5-Phenyl), 129.1 (C6-Phenyl). Anal. Calcd: $C_{19}H_{15}ClN_2O$: C, 70.73; H, 4.68; N, 8.69. Found: C, 70.76; H, 4.71; N, 8.70.

*2.3.5. 5-(2-Chloroquinolin-3-yl)-3-o-tolyl-4,5-dihydroisoxazoline (**4e**)*

R_f = 0.63 in EtOAc/hexane, 3:7. Yellowish brown crystalline solid. m.p.: 154–156 °C; ESI-MS (M^+): 322.04 (100%), 324.12 (37%). FTIR (cm^{-1}): 1638 (C═N, quinoline), 1631 (C═N, isoxazoline), 1236 (–C–O–N), 823 (C–Cl); ^{1}H NMR (400 MHz, DMSO d_6): δ/ppm 2.40 (3H, s, CH_3), 5.94 (1H, t, J = 9.8 Hz, –C–CH–O–), 3.95 (2H, d, J = 9.4 Hz, –C–CH_2–C–), 7.37–8.18 (m, 1H, 2H, 3H, 4H, 5H, 1′H, 3′H, 4′H, 5′H). ^{13}C NMR (200 MHz, DMSO-d_6): δ 156.2 (C1-Isoxazoline), 43.3 (C2-Isoxazoline), 72.7 (C3-Isoxazoline), 18.9 (–CH_3), 150.0 (C1-quinoline), 131.3 (C2-quinoline), 136.5 (C3-quinoline), 127.7 (C4-quinoline), 128.9 (C5-quinoline), 130.2 (C6-quinoline), 126.4 (C7-quinoline), 128.6 (C8-quinoline), 145.8 (C9-quinoline), 129.7 (C1-Phenyl), 138.1 (C2-Phenyl), 129.2 (C3-Phenyl), 131.0 (C4-Phenyl), 126.2 (C5-Phenyl), 129.1 (C6-Phenyl). Anal. Calcd: $C_{19}H_{15}ClN_2O$: C, 70.68; H, 4.71; N, 8.67. Found: C, 70.73; H, 4.74; N, 8.72.

*2.3.6. 5-(2-Chloroquinolin-3-yl)-3-(p-methoxyphenyl)-4,5-dihydroisoxazoline (**4f**)*

R_f = 0.65 in EtOAc/hexane, 3:7. Dark orange solid. m.p.: 157–160 °C; ESI-MS (M^+): 338.10 (100%), 340.08 (32%). FTIR (cm^{-1}): 1634 (C═N, quinoline), 1633 (C═N, isoxazoline), 1235 (–C–O–N), 2827 (–OCH_3), 823 (C–Cl); ^{1}H NMR (400 MHz, DMSO d_6): δ/ppm 3.64 (s, 3H, –OCH_3), 5.92 (1H, t, J = 9.7 Hz, –C–CH–O–), 3.94 (2H, d, J = 9.3 Hz, –C–CH_2–C–), 7.32–8.16 (m, 1H, 2H, 3H, 4H, 5H, 1′H, 2′H, 4′H, 5′H). ^{13}C NMR (200 MHz, DMSO-d_6): δ 156.0 (C1-Isoxazo-

line), 43.4 (C2-Isoxazoline), 72.2 (C3-Isoxazoline), 54.8 (–OCH_3), 150.1 (C1-quinoline), 131.8 (C2-quinoline), 136.3 (C3-quinoline), 127.6 (C4-quinoline), 128.5 (C5-quinoline), 130.4 (C6-quinoline), 126.7 (C7-quinoline), 128.2 (C8-quinoline), 145.9 (C9-quinoline), 126.3 (C1-Phenyl), 120.2 (C2-Phenyl), 114.4 (C3-Phenyl), 164.0 (C4-Phenyl), 114.2 (C5-Phenyl), 130.1 (C6-Phenyl). Anal. Calcd: $C_{19}H_{15}ClN_2O_2$: C, 67.34; H, 4.66; N, 8.29. Found: C, 67.38; H, 4.68; N, 8.31.

2.3.7. 5-(2-Chloroquinolin-3-yl)-3-(p-bromophenyl)-4,5-dihydroisoxazoline (**4g**)

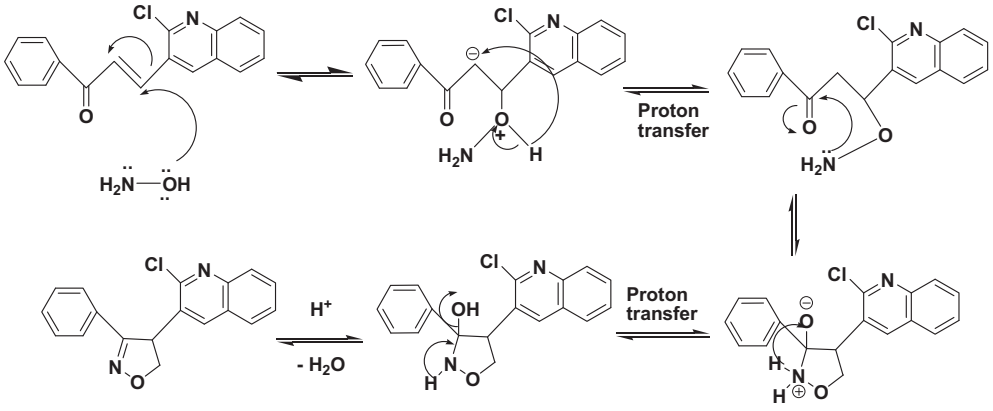
R_f = 0.58 in EtOAc/hexane, 4:6. Orange crystalline solid. m.p.: 171–175 °C; ESI-MS (M^+): 387.12 (100%), 385.08 (36%). FTIR (cm^{-1}): 1636 (C=N, quinoline), 1637 (C=N, isoxazoline), 1242 (–C–O–N), 588 (C–Br), 823 (C–Cl); ^{1}H NMR (400 MHz, DMSO d_6): δ/ppm 5.96 (1H, t, J = 9.8 Hz, –C–CH–O–), 3.98 (2H, d, J = 9.5 Hz, –C–CH_2–C–), 7.37–8.18 (m, 1H, 2H, 3H, 4H, 5H, 1′H, 2′H, 4′H, 5′H). ^{13}C NMR (200 MHz, DMSO-d_6): δ 156.9 (C1-Isoxazoline), 43.7 (C2-Isoxazoline), 72.3 (C3-Isoxazoline), 150.5 (C1-quinoline), 131.7 (C2-quinoline), 136.3 (C3-quinoline), 127.1 (C4-quinoline), 128.2 (C5-quinoline), 130.6 (C6-quinoline), 126.4 (C7-quinoline), 128.0 (C8-quinoline), 145.8 (C9-quinoline), 134.0 (C1-Phenyl), 131.4 (C2-Phenyl), 130.8 (C3-Phenyl), 125.7 (C4-Phenyl), 131.6 (C5-Phenyl), 131.2 (C6-Phenyl). Anal. Calcd: $C_{18}H_{12}BrClN_2O$: C, 55.75; H, 3.18; N, 7.24. Found: C, 55.78; H, 3.22; N, 7.28.

2.3.8. 5-(2-Chloroquinolin-3-yl)-3-(3-nitrophenyl)-4,5-dihydroisoxazoline (**4h**)

R_f = 0.57 in EtOAc/hexane, 3:7. Brown crystalline solid. m.p.: 160–164 °C; ESI-MS (M^+): 353.05 (100%), 355.08 (34%). FTIR (cm^{-1}): 1632 (C=N, quinoline), 1638 (C=N, isoxazoline), 1239 (–C–O–N), 1589 (–NO_2), 823 (C–Cl); ^{1}H NMR (400 MHz, DMSO d_6): δ/ppm 5.97 (1H, t, J = 9.8 Hz, –C–CH–O–), 3.93 (2H, d, J = 9.4 Hz, –C–CH_2–C–), 7.37–8.12 (m, 1H, 2H, 3H, 4H, 5H, 1′H, 3′H, 4′H, 5′H). ^{13}C NMR (200 MHz, DMSO-d_6): δ 156.9 (C1-Isoxazoline), 43.6 (C2-Isoxazoline), 72.4 (C3-Isoxazoline), 150.7 (C1-quinoline), 131.9 (C2-quinoline), 136.5 (C3-quinoline), 127.3 (C4-quinoline), 128.2 (C5-quinoline), 130.4 (C6-quinoline), 126.6 (C7-quinoline), 128.7 (C8-quinoline), 145.8 (C9-quinoline), 140.3 (C1-Phenyl), 130.8 (C2-Phenyl), 122.2 (C3-Phenyl), 150.7 (C4-Phenyl), 122.5 (C5-Phenyl), 130.1 (C6-Phenyl). Anal. Calcd: $C_{18}H_{12}ClN_3O_3$: C, 61.16; H, 3.48; N, 11.87. Found: C, 61.18; H, 3.51; N, 11.88.

3. Results and discussion

We have reported the synthesis of substituted 5-(2-chloroquinolin-3-yl)-3-phenyl-4,5-dihydroisoxazolines from chalcones and hydroxylamine hydrochloride in sodium acetate–acetic acid aqueous solution under ultrasound irradiation. In the first step, 3-(2-chloroquinolin-3-yl)-1-substituted phenyl prop-2-en-1-ones were prepared in excellent yield starting with 2-chloroquinoline-3-carbaldehyde and different substituted ketones in the presence of NaOH in methanol. In the next step, the substituted chalcones were cyclized to dihydroisoxazolines using hydroxylamine hydrochloride under ultrasound irradiation. During the course of cyclization, we have tried to optimise the reaction conditions. The effect of the reaction conditions on the reaction of chalcones and hydroxylamine hydrochloride under ultrasound irradiation was summarized in (Table 1). When the molar ratio of chalcones (**1**): hydroxylamine hydrochloride (**2**) was 1:1, the yield of 5-(2-chloroquinolin-3-yl)-3-phenyl-4,5-dihydroisoxazoline obtained was around 80% (Table 1). By increasing the molar ratio to 1:2, and 1:3 the yields of products were increased to 85% and 89%, respectively (Table 1). The results showed that changing the molar ratio of 1:2 had a significant effect on the yield, and the optimum molar ratio of chalcones: hydroxylamine was found to be 1:3. The important finding was that in the presence of sodium acetate in aqueous acetic acid, the yield of isoxazolines can be increased. It may be due to sodium acetate which is in favour of release of hydroxylamine from hydroxylamine hydrochloride. In order to verify the effect of ultrasound irradiation, we have performed the reaction of chalcone with hydroxylamine hydrochloride by refluxing for 6 h in the absence of ultrasonic waves. The yield of isoxazolines was 76% (Table 1) which was lesser as compared to ultrasonic induced synthesis. While under ultrasound irradiation, the reaction can be completed within 2 h in 88% yield at room temperature (Table 1). Thus, it was clear from the data that, ultrasound could accelerate the reaction of chalcones and hydroxylamine hydrochloride affording more yield than thermal conditions as clears from (Table 1). From the results above, the optimum reaction conditions was chosen: i.e., chalcone (**1**, 2 mmol), hydroxylamine hydrochloride (**2**, 6 mmol), sodium acetate (0.3 mmol). Under this reaction system, a series of experiments for synthesis of 5-(2-chloroquinolin-3-yl)-3-phenyl-4,5-dihydroisoxazoline under 25 kHz ultrasound irradiation were performed. The results are summarized in (Table 1). The reaction may tentatively be visualized to occur via a tandem sequence of reactions depicted in reaction mechanism [24] (Scheme 2) involving (i) attack of oxygen on carbon–carbon double bond forming aminooxy derivative, (ii) attack of nitrogen on carbonyl carbon leading to a five membered ring in either a sequential or a concerted manner, and (iii) proton transfer and removal of water molecule resulting to isoxazoline. Structural features of the synthesized chalcones and isoxazolines were obtained from FTIR, Elemental Analyses, ^{1}H NMR, ^{13}C NMR and mass spectral studies. In the IR spectra of the chalcones, the characteristic absorption



Scheme 2. Probable mechanism for synthesis of 5-(2-chloroquinolin-3-yl)-3-phenyl-4,5-dihydroisoxazoline.

around 1660–1668 cm^{-1} (C=O), 1613–1619 cm^{-1} (CH=CH) which are absent in the spectra of the isoxazoline confirmed the heterocyclization. The ^1H NMR spectrum of the 5-(2-chloroquinolin-3-yl)-3-phenyl-4,5-dihydroisoxazoline in DMSO-d_6 at room temperature using TMS as an internal standard showed the following signals: 5.92–5.97 (1H, t, –C–CH–O–), 3.93–3.99 (2H, d, –C–CH_2–C–) for isoxazoline ring and aromatic protons as multiplet around 7.43–8.27 ppm (m, 10H). The structures were further confirmed by mass spectral studies. They gave molecular ion peaks (M^+) corresponding to the correct molecular formulas.

4. Conclusion

In conclusion, we have developed a practical and cost effective, and environmentally convenient procedure for the synthesis of 5-(2-chloroquinolin-3-yl)-3-phenyl-4,5-dihydroisoxazoline in sodium acetate–acetic acid aqueous solution at room temperature under ultrasound irradiation.

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