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Microwave Assisted Efficient Synthesis of Isoxazolo[5,4-*b*]Quinolines Derivatives

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ABSTRACT

An efficient synthesis for the preparation of isoxazolo[5,4-b]quinolines derivatives was achieved by microwave assisted cyclization of different 2-chloroquinoline-3-carbaldehydes in the presence of $NH_2OH{\cdot}HCl$ and NaOH. This method reduces the reaction times and the products were obtained in good to moderate yields.

Keywords: Isoxazolo[5,4-*b*]quinolones; Microwave irradiation; Quinoline; Isoxazol

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INTRODUCTION

The quinoline skeleton is an important structural motif in natural products, with diverse ranges of pharmacological properties and synthetic interest for chemists due to the role it plays as a building block for preparation of many bioactive compounds [1].

The syntheses of quinolines containing five membered rings have been of interest due to their wide variety of biological and pharmacological properties [2-5]. Among the various derivatives, quinolines possessing isoxazol moiety have been found to be a special framework used to obtain mostly anti-tuberculosis agents [6-8].

In particular, isoxazolo[5,4-*b*]quinolines have received much attention in organic synthesis. Moreover, some derivatives have been shown to display significant analgesic activity [9]. A number of methods for their preparation have been explored; Breitmaier reported the synthesis of 3-phenylisoxazolo[5,4-*b*]quinolines by reaction of o-aminobenzaldehyde with 3-phenyl-2-isoxazolin-5-one [10]. Bhaduri synthetized the isoxazolo[5,4-*b*]quinolines by reacting either 3-acyl, aroyl-2-chloro-6-alkoxy or 6,7-dialkoxyquinolines with hydroxylamine [11]. Recently, Kidway [9] and Shingare [12] reported the synthesis based on the use of acid or base as promoters of cyclization.

However, the search for efficient, clean and short-time methods for the synthesis of this framework is still demanding. In this regard, microwave radiation has become a powerful technique in the field of organic synthesis, due to its importance in decreasing reaction times, increasing product yields and reducing unwanted side reactions compared to conventional synthetic methods [13-17].

Isoxazolo[5,4-*b*]quinolines syntheses using microwave approaches has barely been investigated, only a few derivatives have been performed by nonconventional methods [18]. Very recently, we have reported the synthesis and antibacterial results of a quinoline containing the isoxazol moiety using click chemistry approach [19]. In continuation of our aim to explore new greener protocols for the synthesis of biologically active compounds, herein we report an efficient, clean and rapid method for the synthesis of isoxazolo[5,4-*b*]quinolines derivatives by microwave irradiation.

EXPERIMENTAL SECTION

Melting points were recorded on an Electrothermal 9100 instrument and are uncorrected. IR spectra were obtained with a Nicolet Nexus 470-FTIR spectrometer as KBr pellets and are reported in wavenumbers (cm^{-1}). ^1H NMR and ^{13}C NMR spectra were measured on a Bruker AM-400 spectrometer (400 MHz ^1H NMR and 100 MHz ^{13}C NMR), using $CDCl_3$ and DMSO as solvents. TMS was used as an internal standard. Chemical shifts (δ) and *J* values are reported in ppm and Hz, respectively. Multiplicities are shown as the abbreviations: s (singlet), d (doublet), dd (doublet of doublets), t (triplet), m (multiplet). High resolution mass spectrometry ESI-MS and ESI-MS/MS analyses were conducted in a high resolution hybrid quadrupole (Q) and orthogonal time off light (TOF) mass spectrometer (Waters/Micromass QTOF micro, Manchester, UK) with a constant nebulizer temperature of 100 °C. Reaction progress and the purity of the compounds were monitored by means of TLC using Merck Kieselgel 60 (230–240 mesh). All reagents were purchased from Merck and Sigma Aldrich Co. and used without further purification. All solvents used were dried and distilled prior to use.

General procedure for the preparation of isoxazolo[5,4-*b*]quinoline (3e)

***Conventional method*:** In a round bottom flask a solution of 2-chloroquinoline-3-carbaldehyde **1e** (54 mg, 0.3 mmol), $NH_2OH{\cdot}HCl$ (31 mg, 0.45 mmol), NaOH (72 mg, 1.8 mmol) in ethanol (3 mL) was stirred at room temperature for 20-60 min. After reaction, the solvent was evaporated under reduced pressure. Then the residue was purified by silica gel column chromatography (Petroleum: EtOAc = 70: 30) to give **3e**.

Microwaves methods: In a 10 mL microwave vial, 2-chloroquinoline-3-carbaldehyde **1e** (54 mg, 0.3 mmol), $NH_2OH{\cdot}HCl$ (31 mg, 0.45 mmol) and NaOH (72 mg, 1.8 mmol) were dissolved in ethanol (3 mL). After stirring for 1 min, the vial was closed and heated under microwave irradiation at 100 W for 45-60 seconds. The reaction mixture was filtered and dried over Na_2SO_4. The filtrate was concentrated in vacuo and then purified by recrystallization in ethanol.

6-methylisoxazolo[5,4-*b*]quinoline (3a) This compound was obtained as a white solid; mp 298-300 °C; IR (KBr) ν/cm[1] 1628 (C=N), 1602, 1565, 1505, 1462 (Ar-C=C); ^1H NMR (400 MHz, $CDCl_3$): *δ* 8.53 (s, 1H), 8.34 (s, 1H), 7.89 (d, 1H, *J* = 8.5 Hz), 7.59 (m, 2H), 2.49 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): *δ* 158.8, 146.2, 145.4, 134.4, 134.0, 132.4, 127.1, 126.7, 124.7, 116.4, 21.3; (QTOF-MS) *m/z* calculated for $C_{11}H_8N_2O$: 184.0656, found, 184.0668.

[1,3]dioxolo[4,5-*g*]isoxazolo[5,4-*b*]quinoline (3b) This compound was obtained as a pale yellow solid; mp 231-233 °C; IR (KBr) ν/cm1 1625 (C=N), 1608, 1569, 1482, 1459 (Ar-C=C); ^1H NMR (400 MHz, DMSO-*d*6): *δ* 8.35 (s, 1H), 8.24 (s, 1H), 7.37 (s, 1H), 7.13 (s, 1H), 6.16 (s, 2H); ^{13}C NMR (100, MHz DMSO-*d*6): *δ* 157.7, 151.1, 145.9, 144.2, 142.9, 133.2, 120.5, 114.3, 103.8, 103.7, 101.9; (QTOF-MS) *m/z* calculated for $C_{11}H_6N_2O_3$: 214.0412, found, 214.0423.

6-methoxyisoxazolo[5,4-*b*]quinoline (3c) This compound was obtained as a white solid; mp 280-282 °C; IR (KBr) ν/cm1 1628 (C=N), 1615, 1559, 1505, 1459 (Ar-C=C); ^1H NMR (400 MHz, DMSO-*d*6): *δ* 8.45 (s, 1H), 8.28 (s, 1H), 7.80 (d, 1H, *J* = 9.2 Hz), 7.40 (dd, 1H, *J* = 9.0, 2.6 Hz), 7.10 (d, 1H, *J* = 2.7 Hz), 3.84 (s, 3H); ^{13}C NMR (100 MHz, DMSO-*d*6): *δ* 157.3, 156.0, 143.0, 142.0, 133.2, 128.0, 125.3, 122.0, 117.2, 107.0, 55.4; (QTOF-MS) *m/z* calculated for $C_{11}H_8N_2O_2$: 200.0641, found, 200.0956.

5,7-dimethylisoxazolo[5,4-*b*]quinoline (3d) This compound was obtained as a white solid; mp 250-252 °C ; IR (KBr) ν/cm1 1622 (C=N), 1597, 1575, 1493, 1443 (Ar-C=C); ^1H NMR (400 MHz, DMSO-*d*6): *δ* 8.49 (s, 1H), 8.29 (s, 1H), 7.40 (s, 1H), 7.12 (s, 1H), 2.57 (s, 3H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, DMSO-*d*6): *δ* 158.4, 146.7, 143.0, 140.2, 134.9, 130.5, 127.4, 124.3, 121.7, 115.6, 21.4, 18.3; (QTOF-MS) *m/z* calculated for $C_{12}H_{10}N_2O$: 198.0833, found, 198.0849.

Isoxazolo[5,4-*b*]quinoline (3e) This compound was obtained as a white solid; mp 175-177 °C ; IR (KBr) ν/cm1 1623 (C=N), 1601, 1575, 1486, 1462 (Ar-C=C); ^1H NMR (400 MHz, $CDCl_3$): *δ* 8.53 (s, 1H), 8.42 (s, 1H), 7.98 (d, 1H, *J* = 8.3 Hz), 7.82 (d, 1H, *J* = 8.0 Hz), 7.79 (m, 1H), 7.59 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 159.4, 153.3, 146.9, 146.7, 143.0, 119.3, 115.9, 104.9, 103.1, 102.2; (QTOF-MS) *m/z* calculated for $C_{10}H_6N_2O$: 170.0511, found, 170.0523.

5,8-dimethylisoxazolo[5,4-*b*]quinoline (3f) This compound was obtained as white solid; mp 286-288 °C ; IR (KBr) ν/cm11625 (C=N), 1608, 1570, 1495, 1476 (Ar-C=C); ^1H NMR (400 MHz, $CDCl_3$): *δ* 8.57 (s, 1H), 8.06 (s, 1H), 7.49 (m, 1H), 7.31 (m, 1H), 2.64 (s, 3H), 2.63 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 158.9, 146.3,

145.5, 134.4, 134.0, 132.4, 127.2, 126.8, 124.7, 116.5, 21.3, 14.6; (QTOF-MS) *m/z* calculated for $C_{12}H_{10}N_2O$: 198.08, found, 198.17.

5,8-dimethoxyisoxazolo[5,4-*b*]quinoline (3g) This compound was obtained as a white solid; mp 187-189 °C ; IR (KBr) ν/cm1 1628 (C=N), 1615, 1572, 1506, 1456 (Ar-C=C); ^{1}H NMR (400 MHz, DMSO-*d*6): δ 8.41 (s, 1H), 8.35 (s, 1H), 7.00 (d, 1H, *J* = 8.8 Hz), 6.79 (dd, 1H, *J* = 8.8, 1.5 Hz), 3.98 (s, 3H), 3.94 (s, 3H); ^{13}C NMR (400 MHz, DMSO-*d*6): δ 158.4, 153.6, 149.3, 148.4, 147.6, 139.8, 135.5, 119.1, 113.6, 107.0, 56.3, 56.2; (QTOF-MS) *m/z* calculated for $C_{12}H_{10}N_2O_3$: 230.0777, found, 230.0794.

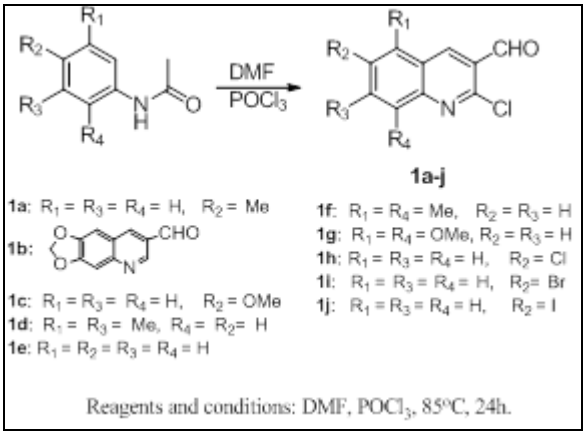
6-chloroisoxazolo[5,4-*b*]quinoline (3h) This compound was obtained as a white solid; mp 165-168 °C ; IR (KBr) ν/cm1 1623 (C=N), 1600, 1555, 1506, 1450 (Ar-C=C); ^{1}H NMR (400 MHz, DMSO-*d*6): δ 8.54 (s, 1H), 8.31 (s, 1H), 7.99 (d, 1H, *J* = 9.3 Hz), 7.85 (s, 1H), 7.74 (dd, 1H, *J* = 8.0, 2.0 Hz); ^{13}C NMR (100 MHz, DMSO-*d*6): δ 156.2, 151.3, 146.1, 138.6, 133.8, 132.3, 130.5, 127.4, 127.0, 126.6; (QTOF-MS) *m/z* calculated for $C_{10}H_5ClN_2O$: 204.0110, found, 204.0119.

6-bromoisoxazolo[5,4-*b*]quinoline (3i) This compound was obtained as a white solid; mp 213-215 °C ; IR (KBr) ν/cm1 1626 (C=N), 1599, 1558, 1501, 1467 (Ar-C=C); ^{1}H NMR (400 MHz, DMSO-*d*6): δ 8.59 (s, 1H), 8.26 (s, 1H), 8.09 (d, 1H, *J* = 2.0 Hz), 7.96 (m, 1H), 7.87 (s, 1H),; ^{13}C NMR (100 MHz, DMSO-*d*6): δ 158.1, 153.6, 147.8, 139.7, 131.6, 130.4, 128.5, 127.7, 127.1, 122.6; (QTOF-MS) *m/z* calculated for $C_{10}H_5BrN_2O$: 247.96, found, 248.04.

6-iodoisoxazolo[5,4-*b*]quinoline (3j) This compound was obtained as a white solid; mp 260-262 °C ; IR (KBr) ν/cm1 1628 (C=N), 1602, 1569, 1506, 1459 (Ar-C=C); ^{1}H NMR (400 MHz, DMSO-*d*6): δ 8.55 (s, 1H), 8.31(s, 1H), 8.29 (d, 1H, *J* = 1.5 Hz), 8.05 (dd, 1H, *J* = 8.8, 2.0 Hz), 7.81 (d, 1H *J* = 9.3 Hz); ^{13}C NMR (100 MHz, DMSO-*d*6): δ 155.4, 150.6, 146.7, 140.3, 138.5, 136.4, 130.5, 128.9, 128.2, 95.3; (QTOF-MS) *m/z* calculated for $C_{10}H_5IN_2O$: 295.9481, found, 295.9493.

RESULTS AND DISCUSSION

The starting materials 2-chloroquinolin-3-carbaldehydes were easily prepared with Vilsmeier reagent (DMF + $POCl_3$), according to procedures already described in the literature [19-20].

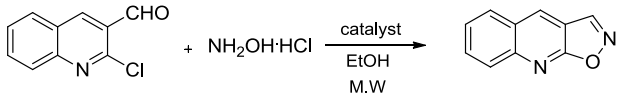


Scheme 1: Preparation of 2-chloro-quinolin-3-carbaldehydes

The synthesis of the title compounds was carried out by microwave irradiation in a CEM Discover microwave synthesis apparatus. In order to optimize the reaction, 2-chloroquinoline-3-carbaldehyde **1** and hydroxylamine **2** in ethanol were selected as a model reaction under different catalytic conditions to afford the isoxazolo[5,4-*b*]quinoline derivative **3** (Table 1). The best results were obtained by using NaOH (Table 1, entry 2) under the following conditions: 6 equiv of catalyst at 100 W for 45 seconds.

Furthermore, we also investigated the use of K_2CO_3 and AcOH reported by Shingare [12] and Kidwai [9], but the yields were reduced to 12 and 45%, respectively (Table 1, entry 1, 4). When Et_3N was used, a low yield was obtained (Table 1, entry 3). Finally, we investigated the scope of this reaction by using Lewis acid and *Brønsted* acid (Table 1, entry 5, 6) but no reaction was observed.

Table 1: Optimization of reaction conditions for 3e

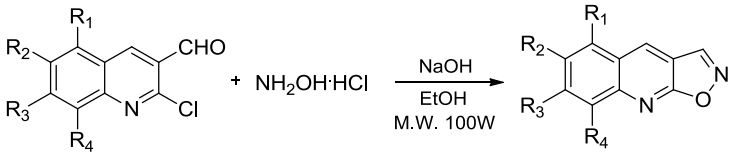


Entry	Catalyst	Yielda (%)
1	K2CO3	12
2	NaOH	85
3	Et3N	35
4	AcOH	45
5	InCl3	NRb
6	TFA	NRb

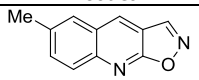
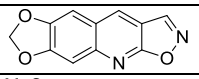
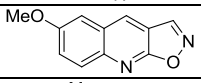
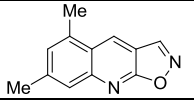
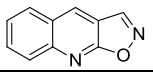
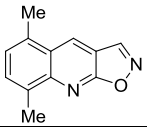
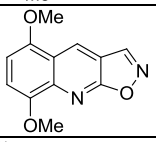
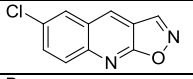
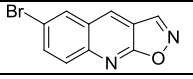
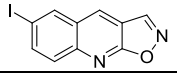
[a]Isolated yield. [b]No reaction

By using the optimized conditions (Table 1, entry 2) in order to reveal the generality of this method, different 2-chloroquinoline-3-carbaldehydes were explored to investigate the electron donating and electron with drawing groups effects on the quinoline ring to obtain the desired products. The reactions were performed either under microwave irradiation or conventional synthesis. The results are depicted in Table 2.

Table 2: Preparation of substituted isoxazolo[5,4-*b*]quinolines 3a-j

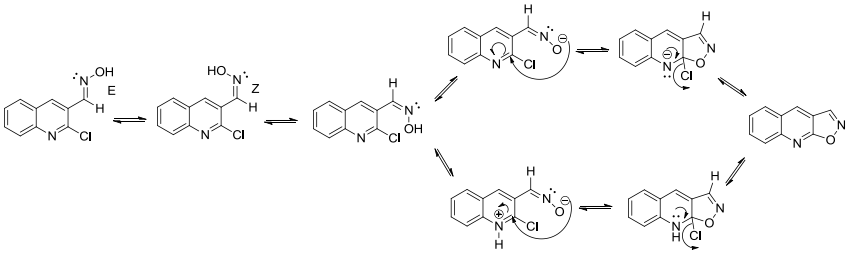


1a-j 2 3a-j

Entry	Product	Time	Yield (%)	MP (°C)
1		A= 25 min; B= 50 s	A= 67; B= 91	298-300
2		A= 45 min; B= 60 s	A= 48; B= 85	231-233
3		A= 30 min; B= 60 s	A= 68; B= 88	280-282
4		A= 40 min; B= 50 s	A= 71; B= 92	250-252
5		A= 20 min; B= 45 s	A= 73; B= 94	175-177
6		A= 40 min; B= 55 s	A= 68; B= 89	286-288
7		A= 60 min; B= 60 s	A= 61; B= 85	187-189
8		A= 90 min; B= 60 s	A= 41; B= 81	165-168
9		A= 90 min; B= 60 s	A= 35; B= 85	213-215
10		A= 90 min; B= 60 s	A= 39; B= 83	260-262

A: conventional synthesis. B: microwave-assisted. [a]Isolated yield

Some interesting points of this method include: (1) the ready access to isoxazolo[5,4-*b*]quinolines derivatives in comparison to conventional synthesis (Table 2, methods A and B); (2) High yields in comparison to conventional synthesis (Table 2, methods A or B) and (3) all the pure products were obtained by filtration and recrystallization in ethanol. The proposed mechanism for the formation of isoxazolo[5,4-*b*]quinoline derivatives is illustrated in Scheme 2. Finally, the synthesized products were characterized by FTIR, ^{1}H NMR, ^{13}C NMR and mass spectroscopy studies.



Scheme 2: Proposed mechanism for the formation of 3e

CONCLUSION

We have demonstrated that microwave assisted reaction of hydroxylamine with different substituted 2-chloro-3-quinolin-3-carbaldehyde in the presence of NaOH reliably yields isoxazolo[5,4-*b*]quinolines derivatives. These conditions allowed the synthesis of the title compounds in good yields and short times compared to previous methods. Further biological studies are currently being undertaken and will be reported in due course.

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