

Microwave Irradiation And Their Advantages In Synthesis Of Quinoline Bearing Isoxazoles Nucleus

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ABSTRACT

In this study, solvent-free conditions coupled with microwave irradiation and their advantages in synthesis of quinoline derivatives were reported. Consequently, microwave irradiation significantly reduced reaction times compared to traditional heating methods. A mild and simple method for synthesis of important isoxazole[5,4-b] quinolines 3a-e is reported from 2-chloro-3-formylquinoline and hydroxylamine through a single step synthesis. Particularly synthesis by solvent-free solid supported microwave irradiation was found more eco-friendly.

Keywords: Microwave, Quinolines, Isoxazole, Condensation, Microbial.

INTRODUCTION

In recent year there has been a growing interest of the application of microwave heating in organic chemistry [1, 2] due to its remarkable advantages such as decrease in the reaction time, cleaner reaction, easier workup, better yield and mainly eco-friendly. It has been commonly employed as thermal energy source in various organic reactions [3-4]. The exploitation of microwaves for assisting different organic reactions, has blossomed into an important tool in synthetic organic chemistry with large horizon of applications. Due to the timeliness, ease of workability and eco-friendly, microwaves provide an alternative to environmentally unacceptable procedures, which may be time-consuming or use toxic and expensive reagents. Day to day there is considerable interest in rapid chemical synthesis under microwave reactor.

Quinoline and isoxazole have been found to be associated with diverse biological activities and numerous reports have appeared in the literature [5-8]. Which highlighted their chemistry and use. The quinoline derivatives have remarkable pharmacological activity [9-11] and widely used in the field of anti-malarial drugs[12-14]. Isoxazole derivatives were shown to possess many biological activities including anti-inflammatory [15], anti-bacterial [16], antibiotic[17], anticonvulsant[18], antitubercular[19], antifungal [20] and anxiolytic activity [21]. Isoxazoles are easily available and have high chemical reactivity. A series of heterocyclic compounds containing a five membered ring consisting of three carbon atoms united to first position oxygen and second position nitrogen atom .Substituted

Isoxazoles are important compounds of many drugs & drug candidates. This survey was attempted to summarize the synthetic methods and reactions of isoxazoles.

In continuation of our interest in exploiting the use of microwave irradiation [22-26], we proposed to synthesise a series of isoxazolo[5,4-*b*]quinolines **3a-g** using 2-chloro-3-formylquinolines (**1a-g**) and hydroxylamine hydrochloride (**2**).

EXPERIMENTAL

Melting points (mp) were determined using Boetius micro heating table and are uncorrected. IR (KBr, cm^{-1}) spectra were obtained on Shimadzu-8201 spectrometer.

$^1\text{H-NMR}$ and $^{13}\text{C-NMR}$ spectra were recorded on Bruker AMX-400 MHz spectrometer using TMS as an internal reference (Chemical shifts in δ , ppm). Elemental analyses were performed on Perkin Elmer CHN-analyzer. Mass spectra were recorded on Shimadzu GCMS-QP5050A (70 eV) mass spectrometer. For microwave irradiation a Kenstar (OM-20ESP, 2450 MHz) domestic microwave oven was used.

General procedure for the preparation of isoxazolo[5,4-*b*]quinolines (**3a-g**):

2-Chloro-3-formylquinolines (1 mmol), hydroxylamine hydrochloride (1.25 mmol) and PTSA (120 mg) were taken in 100 ml beaker and mixed well. Then the reaction mixture was irradiated in microwave oven for the respective time (**Table 1**).

Table 1. Physical data of isoxazolo[5,4-*b*]quinolines (3a-g**)**

Compound	Time (min)	Yield (%)	mp° C
3a	4	90	188
3b	3	89	174
3c	3	90	195
3d	6	79	190
3e	5	85	197
3f	6	75	168
3g	8	78	211

After completion of the reaction, the mixture was poured into ice. The formed product was extracted with chloroform and purified using column chromatography. Structure of target compound confirmed by FTIR, $^1\text{HNMR}$, $^{13}\text{C-NMR}$, Mass spectra and elemental analysis (**Table 2**).

Table 2 – Spectral characterization and elemental analysis data of compounds 3a-g

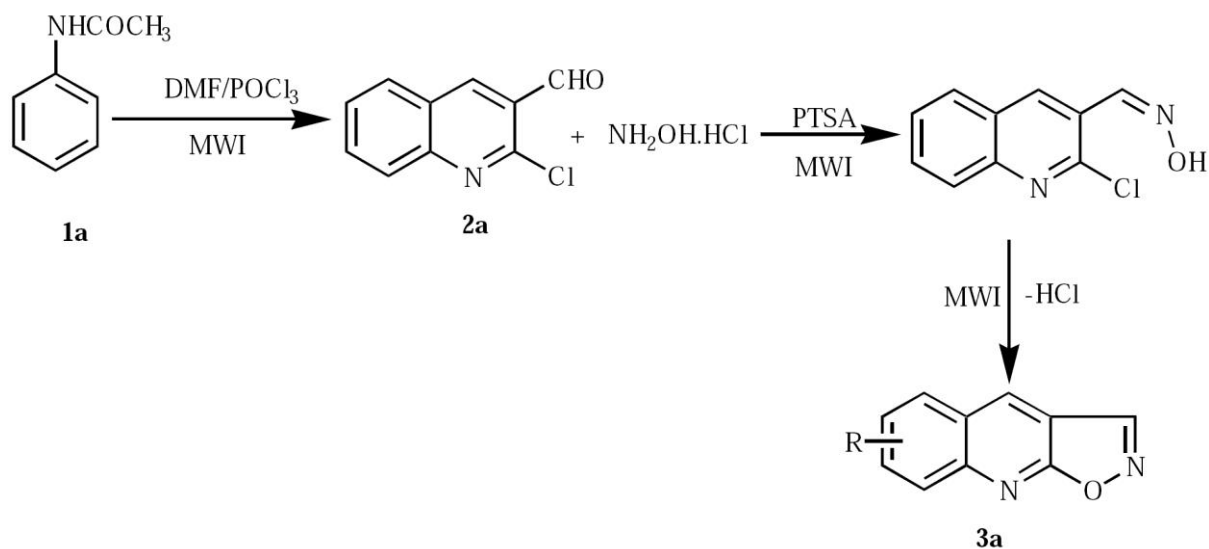
Compd	¹ H NMR (DMSO-d ₆) (δ ppm)	C	H Found (Calcd)	N	MS (70 eV) M+. (m/z)
3a	7.39-8.21 (m, 4H, Ar-H), 8.26 (s, 1H, C ₄ -H), 8.45 (s, 1H, C ₃ -H)	70.57, (70.59)	3.55 (3.56)	16.49 (16.46)	170
3b	2.51 (s, 3H, C ₆ -CH ₃), 7.20-8.04 (m, 2H, Ar- H), 8.11 (s, 1H, C ₅ -H), 8.22 (s, 1H, C ₄ -H), 8.48 (s, 1H, C ₃ -H)	71.70 (71.74)	4.31 4.38	15.28 (15.22)	184
3c	2.58 (s, 3H, C ₈ -CH ₃), 7.18-8.18 (m, 3H, Ar- H), 8.25 (s, C ₄ -H), 8.53 (s, C ₃ -H)	77.75 (71.74)	4.38 4.38	15.29 (15.22)	184
3d	3.93 (s, 3H, C ₆ -OCH ₃), 7.16-7.97 (m, 4H, Ar- H), 8.10 (s, 1H, C ₅ -H), 8.22 (s, 1H, C ₄ -H), 8.59 (s, 1H, C ₃ -H)	66.96 (66.00)	4.08 4.03	14.01 (14.00)	200
3e	3.96 (s, 3H, C ₈ -OCH ₃), 7.12-7.97 (m, 3H, Ar- H), 8.30 (s, 1H, C ₄ -H), 8.65 (s, 1H, C ₃ -H)	66.03 (66.00)	4.07 4.03	14.08 (14.00)	200
3f	7.16-8.22 (m, 8H, Ar-H), 8.38 (s, 1H, C ₄ -H), 8.56 (s, 1H, C ₃ -H)	58.80 (58.82)	2.41 (2.47)	13.68 (13.73)	204
3g	7.22-8.08 (m, 8H, Ar-H), 8.25 (s, 1H, C ₄ -H), 8.59 (s, 1H, C ₃ -H)	48.09 (48.19)	2.09 (2.02)	11.22 (11.24)	248

RESULTS AND DISCUSSION

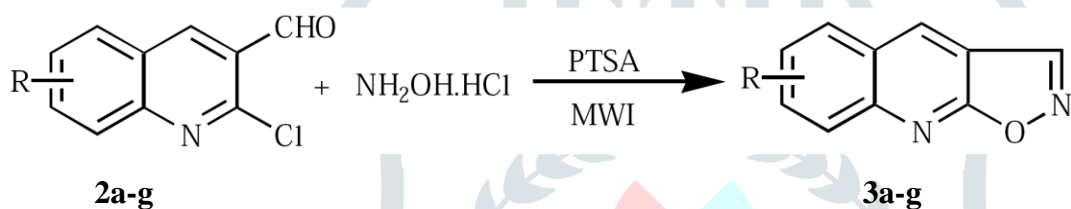
The title compounds were synthesized through the reaction sequence shown in **Scheme 1**. The key intermediate 2-chloro-3-formylquinoline was synthesized by Vilsmeier-Haack reaction of acetanilides. When irradiation of 2-chloro-3-formylquinoline with hydroxylamine hydrochloride in presence of *p*-toluene sulphonic acid at 160 W for 4 min. under microwave reactor. The single target compound obtained 90% yield. The formation of target compound confirmed by FTIR, ¹H-NMR, ¹³C-NMR, Mass spectra and elemental analysis.

IR spectrum of **3a** showed the disappearance of absorption at 1680 cm⁻¹ corresponding to >C=O group and exhibited absorptions at 1430 cm⁻¹ for >C-O- group and 1560cm⁻¹ for -NO- group. ¹H-NMR spectrum recorded two singlets at δ 8.26 and δ 8.45 for C₄, C₃-H protons and other aromatic protons registered multiplet in the region δ 7.39-8.21.

The mass spectrum showed a molecular ion peak at *m/z* 170. So the structure of the compound **3a** was confirmed as isoxazolo[5,4-*b*]quinoline (**Scheme 1**). A similar series of isoxazolo[5,4-*b*]quinolines **3b-g** were prepared and characterized (**Scheme 2**).



Scheme 1



Scheme 2

3a: R = H,**3b:** R = 6-CH₃,**3c:** R = 8-CH₃,**3d:** R = 6-OCH₃,**3e:** R = 8-CH₃,**3f:** R = 6-CL,**3g:** R = 6-Br

Conclusion

In conclusion, the salient feature of our approach is coupling microwaves with solvent free technique keeping modernization and simplification of classical procedure, avoiding volatile and toxic organic solvents, corrosive, mineral acids which make it a clean, efficient and cheap technology to isoxazole quinolines.

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