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COMPARATIVE STUDY ON CONVENTIONAL HEATING, ULTRASONICATION AND MICROWAVE ASSISTED SYNTHESIS OF 2-AMINO-1-ALKYL-4-OXO-1,4-DIHYDROQUINOLINE-3-CARBONITRILES

Fereshteh Khoramdelan, Abolghasem Davoodnia[**], Mohammad R. Bozorgmehr, and Mahmoud Ebrahimi

Department of Chemistry, Mashhad Branch, Islamic Azad University, Mashhad 9175687119, Iran

Abstract: In present study, the synthesis of 2-amino-1-alkyl-4-oxo-1,4-dihydroquinoline-3-carbonitriles by the reaction of *N*-alkylisatoic anhydrides with malononitrile using conventional heating method in pyridine is compared with unconventional approaches including ultrasonication in pyridine and microwave irradiation. The results showed that although the reactions completed within shorter period of time under microwave irradiation, the yields of the products were higher under conventional heating and ultrasonication in pyridine. However, the conventional heating method has longer reaction times than others.

Keywords: 1,4-Dihydroquinolines, *N*-Alkylisatoic anhydrides, Ultrasonic irradiation, Microwave irradiation

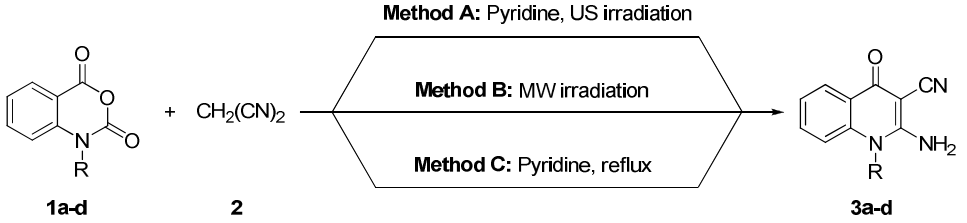
Introduction

Polyfunctionalized heterocyclic compounds play important roles in the drug discovery process, and important structural components in both biologically active and natural compounds. Therefore, it is not surprising that research on the synthesis of polyfunctionalized heterocyclic compounds has received significant attention. Functionalized quinolines have been an object of great interest to organic and medicinal scientists over many years, as they are present in a number of important organic compounds which exhibit diverse and interesting biological activities such as antibacterial[i], antifungal[i], antioxidant[ii], antimalarial[iii], anticancer[iv,v], antiviral[vi], antinociceptive[vii], anti-inflammatory[vii], and analgesic[viii] activities. Also, a number of compounds with quinoline motif are known as potential inhibitors of nucleotide pyrophosphatase[ix], HIV-1[x], topoisomerase I[xi], HDAC class I[xii], *β*-glucuronidase[xiii], MvfR[xiv], *α*-amylase[xv], VEGFR-II[xvi], and COX-2[xvii]. Furthermore, various derivatives of these compounds are substantially useful as chemotherapeutic agents for leishmaniasis[xviii].

[*]Corresponding author. Tel.: +98-51-38435000; Fax: +98-51-38429520; E-mail: adavoodnia@mshdiau.ac.ir; adavoodnia@yahoo.com

In recent years, the application of ultrasonic (US) and microwave (MW) irradiation as very significant nonconventional techniques in organic synthesis have attracted much research interest because of the simplicity in operation and enhanced reaction rates[xix-xxii]. Other attractive features of these protocols are formation of purer products in high yields, mild reaction conditions, reduced energy consumption, and enhanced selectivity, compared with conventional heating method[xxiii-xxvi].

Inspired by these facts and due to our interest in the synthesis of heterocyclic compounds[xxvii-xxxix], and in continuation of our previous works in the application of US and MW irradiation in organic reactions[xl-xliv], herein the efficiency of US and MW irradiation, as nonconventional clean energy sources, are compared with conventional heating method for the synthesis of some new 2-amino-1-alkyl-4-oxo-1,4-dihydroquinoline-3-carbonitriles **3a-d** by the reaction of *N*-alkylisatoic anhydrides **1a-d** with malononitrile **2** (Scheme 1). To the best of our knowledge, this is the first report with such studies.



a: R = Me
b: R = Et
c: R = n-Bu
d: R = CH_2Ph

Scheme 1. Synthesis of 2-amino-1-alkyl-4-oxo-1,4-dihydroquinoline-3-carbonitriles using US irradiation (Method A), MW irradiation (Method B), and conventional heating (Method C)

Experimental

All chemicals were purchased from Merck and Aldrich and used without purification. Ultrasonication was performed by Soltec sonicator (Italy, 2200ETH S3) at a frequency of 40 kHz and a nominal power of 260 W. Microwave irradiation was done using Milestone microwave oven (MicroSYNTH). Melting points were measured on a Stuart SMP3 melting point apparatus. IR spectra were recorded on a Tensor 27 Bruker spectrophotometer in KBr disks. The ^1H and ^{13}C NMR spectra were measured on a Bruker 300 spectrometer at 300 and 75 MHz frequencies for ^1H and ^{13}C, respectively.

General procedure for the synthesis of 2-amino-1-alkyl-4-oxo-1,4-dihydroquinoline-3-carbonitriles 3a-d.

Method A. A mixture of *N*-alkylisatoic anhydrides **1a-d** (1 mmol) and malononitrile **2** (1 mmol) in pyridine (2 mL) was sonicated at 60 °C for 45 min. After the completion of the reaction, the solvent was evaporated under reduced pressure. The crude product was collected and washed with diethyl ether, and water to give the pure products **3a-d** in high yields.

Method B. A mixture of *N*-alkylisatoic anhydrides **1a-d** (1 mmol), malononitrile **2** (1 mmol) and a few drops of acetone was subjected to microwave irradiation at 1000 W for 10 min. After the completion of the reaction, diethyl ether was added and the precipitate was filtered off. The crude product was washed with dichloromethane and water, respectively, to give the pure products **3a-d** in high yields.

Method C. A mixture of *N*-alkylisatoic anhydrides **1a-d** (1 mmol) and malononitrile **2** (1 mmol) in pyridine (2 mL) was heated under reflux for 3 h. Upon completion of the transformation, the solvent was removed under reduced pressure. The residue was washed with diethyl ether, and water to give the pure products **3a-d** in high yields.

2-Amino-1-methyl-4-oxo-1,4-dihydroquinoline-3-carbonitrile (3a): FT-IR (KBr disk, υ, cm^{-1}): 3334 and 3224 (NH_2), 2217 (CN), 1654 (C=O). ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 3.63 (s, 3H, NCH_3), 7.15 (s br, 2H, NH_2), 7.20-8.00 (m, 4H, arom-H); ^{13}C NMR (75 MHz, DMSO-d_6, δ, ppm): 33.9, 76.1, 117.5, 117.6, 121.9, 123.5, 125.2, 132.9, 138.3, 156.7, 175.5.

2-Amino-1-ethyl-4-oxo-1,4-dihydroquinoline-3-carbonitrile (3b). FT-IR (KBr disk, υ, cm^{-1}): 3338 and 3220 (NH_2), 2210 (CN), 1665 (C=O). ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.25 (t, J = 6.9 Hz, 3H, CH_3), 4.23 (q, J = 6.9 Hz, 2H, CH_2), 7.31-7.38 (m, 1H, arom-H), 7.63 (s br, 2H, NH_2), 7.67-7.72 (m, 2H, arom-H), 8.07-8.12 (m, 1H, arom-H). ^{13}C NMR (75 MHz, DMSO-d_6, δ, ppm): 13.1, 31.1, 76.9, 116.2, 117.9, 123.6, 123.7, 125.8, 133.2, 139.0, 156.4, 174.2.

2-Amino-1-butyl-4-oxo-1,4-dihydroquinoline-3-carbonitrile (3c). FT-IR (KBr disk, υ, cm^{-1}): 3345 and 3213 (NH_2), 2211 (CN), 1672 (C=O). ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 0.94 (t, J = 7.2 Hz, 3H, CH_3), 1.38-1.51 (m, 2H, CH_2), 1.55-1.67 (m, 2H, CH_2), 4.15 (t, J = 8.1 Hz, 2H, CH_2), 7.34 (t, J = 7.5 Hz, 1H, arom-H), 7.61-7.75 (m, 4H, NH_2 and arom-H), 8.09 (dd, J = 7.8, 1.5 Hz, 1H, arom-H). ^{13}C NMR (75 MHz, DMSO-d_6, δ, ppm): 14.2, 19.3, 29.4, 44.5, 77.0, 116.4, 117.9, 123.6, 123.7, 125.8, 133.2, 139.2, 156.6, 174.2.

2-Amino-1-benzyl-4-oxo-1,4-dihydroquinoline-3-carbonitrile (3d). FT-IR (KBr disk, υ, cm^{-1}): 3392 and 3334 (NH_2), 2204 (CN), 1663 (C=O). ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 5.55 (s, 2H, CH_2), 7.15 (d, J = 7.2 Hz, 2H, arom-H), 7.26-7.46 (m, 5H, arom-H), 7.54-7.61 (m, 1H, arom-H), 7.74 (s br, 2H, NH_2), 8.11 (dd, J = 7.8, 1.5 Hz, 1H, arom-H). ^{13}C NMR (75 MHz, DMSO-d_6, δ, ppm): 48.0, 77.1, 116.9, 117.8, 123.7, 126.3, 127.8, 129.2, 133.1, 135.6, 136.6, 139.6, 150.0, 157.4, 174.3.

Results and discussion

The starting materials, *N*-alkylisatoic anhydrides **1a-d**, were prepared according to the literature methods[xlv,xlvi]. Advantages of performing organic reactions under nonconventional conditions prompted us to study the synthesis of 2-amino-1-alkyl-4-oxo-1,4-dihydroquinoline-3-carbonitriles **3a-d** under US and MW irradiation. First, compounds **1a-d** were treated with malononitrile **2** in pyridine under US irradiation at 60 °C (Method A) or in a few drops of acetone under MW irradiation at 1000 W (Method B). Monitoring of the reactions with thin-layer chromatography (TLC) showed that the reactions were completed within 45 min in method A and 10 min in method B, giving high yields of the products identified as 2-amino-1-alkyl-4-oxo-1,4-dihydroquinoline-3-carbonitriles **3a-d**. Although, the reactions were completed within shorter period of time under MW irradiation (Method B), the reaction yields were higher under US irradiation (Method A).

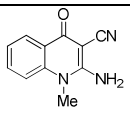
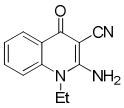
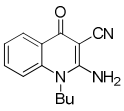
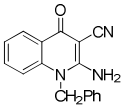
The structural assignments of the products **3a-d** were based upon the spectral data. For example, ^1H NMR spectrum of **3c** in DMSO-d_6 demonstrated a triplet at δ 0.94 ppm (3H, J = 7.2 Hz) for methyl group, two multiplets at δ 1.38-1.51 and 1.55-1.67 ppm for two methylene groups, a triplet at δ 4.15 ppm (2H, J = 8.1 Hz) for N-CH_2, and other characteristic signals at δ 7.34-8.09 ppm assigned to aromatic protons overlapped with NH_2 group, indicating the formation of the product **3c**. The IR spectrum of **3c** shows NH_2 absorption bands at 3345 and

3213 cm^{-1}, and a sharp band at 2211 cm^{-1} for CN, in addition to a band at 1672 cm^{-1} for C=O group. Furthermore, the ^{13}C NMR spectrum showed the characteristic signals at δ 14.2, 19.3, 29.4, 44.5, 77.0, 116.4, 117.9, 123.6, 123.7, 125.8, 133.2, 139.2, 156.6, and 174.2 ppm which are in accord with structure **3c**.

In order to draw a comparison between nonconventional and conventional heating for preparation of compounds **3a-d**, a mixture of **1a-d** and **2** in pyridine was heated under reflux for 3 h (Table 1). By comparing the data in Table 1, it is obvious that the US (Method A) and MW (Method B) irradiation approaches for the synthesis of compounds **3a-d** are faster than conventional heating (Method C). However, the yields in methods A and C were higher than B.

Table 1

Comparison of times and yields on the formation of compounds **3a-d** using US irradiation, MW irradiation and conventional heating[a]

Entry	R	Product	Method A (US irradiation)		Method B (MW irradiation)		Method C (Conventional heating)		mp (°C)
			Time (min)	Yield (%)	Time (min)	Yield (%)	Time (min)	Yield (%)	
1	Me	 **3a**	45	96	10	78	180	95	332-334
2	Et	 **3b**	45	95	10	78	180	91	318-320
3	n-Bu	 **3c**	45	90	10	68	180	90	305-307
4	CH_2Ph	 **3d**	45	95	10	70	180	91	310-312

[a]Reaction conditions: *N*-alkylisatoic anhydrides **1a-d** (1 mmol) and malononitrile **2** (1 mmol) in pyridine (2 mL) under US irradiation at 60 °C (Method A), or in a few drops of acetone under MW irradiation at 1000 W (Method B), or in pyridine (2 mL) under reflux (Method C).

Conclusion

In summary, 2-amino-1-alkyl-4-oxo-1,4-dihydroquinoline-3-carbonitriles **3a-d** were synthesized by the reaction of *N*-alkylisatoic anhydrides **1a-d** with malononitrile **2** under various reaction conditions including US irradiation in pyridine at 60 °C (Method A), MW irradiation in a few drops of acetone at 1000 W (Method B), and also conventional heating in refluxing pyridine (Method C). In comparison, the reactions carried out with the assistance of US and MW techniques are faster than conventional heating. The yields of the products in methods A and C were higher than B.

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