Microwave-assisted synthesis of quinoline alkaloids: 4-Methoxy-1-methyl-2-quinolinone and its analogs

Vetrivel Nadaraj, Senniappan Thamarai Selvi,* and Raju Sasi

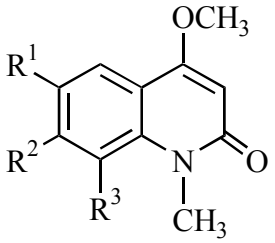
Department of Chemistry (PG & Research) Kongunadu Arts & Science College G.N.Mills Post, Coimbatore-641 029, INDIA
E-mail: thamaraimohan@yahoo.co.in

Abstract
The microwave-induced synthesis of some quinoline alkaloids of the type 4-methoxy-1-methyl-2-quinolinone including folimine is reported. The precursors 4-hydroxy-2-quinolinone derivatives were effectively prepared in a single step from aniline and diethylmalonate using *p*-toluenesulfonic acid as a catalyst and these intermediates were converted to the titled quinoline alkaloids by treatment with dimethyl sulfate, N,N-dimethylformamide and potassium carbonate. The presented synthentic procedure is a convenient, simple and fast alternative for synthesizing 4-methoxy-1-methyl-2-quinolinone and its derivatives.

Keywords: Quinolines, microwave irradiation, 4-hydroxy-2-quinolinones, 4-methoxy-1-methyl-2-quinolinones

Introduction

The root stock of quinoline alkaloids is specific to the plant family *Rutaceae* embodying about hundred and fifty genera with sixteen hundred species. The presence of quinoline nucleus in the framework of various pharmacologically active compounds with antiasthmatic,[1] antibacterial,[2] antifungal,[3] antimalarial,[4] anti-viral,[5] anti-inflammatory[6] activities continue to promote their synthetic efforts. Among the quinolines, some facile precursors are available which could be transformed into desired quinoline alkaloids using various reactions.[7-9] For instance, 4-hydroxy-2-quinolinone is an important biosynthetic[7] and synthetic[8,9] precursor of quinoline alkaloids. Methylated compounds of this type like 4-methoxy-1-methyl-2-quinolinone (**1**), folimine (**2**), 4,6-dimethoxy-1-methyl-2-quinolinone and 4,7,8-trimethoxy-1-methyl-2-quinolinone (Scheme 1) are widely distributed in nature.[10-13] Though these alkaloids are natural products, they are also used as synthetic intermediates for the preparation of other quinoline alkaloids[14] and polyheterocycles.



1 $R^1=R^2=R^3=$ H; 4-Methoxy-1-methyl-2-quinolinone

2 $R^1=R^2=$ H, $R^3=OCH_3$; Folimine

3 $R^2=R^3=$ H, $R^1=OCH_3$; 4,6-Dimethoxy-1-methyl-2-quinolinone

4 $R^1=$ H, $R^2=R^3=OCH_3$; 4,7,8-Trimethoxy-1-methyl-2-quinolinone

Scheme 1

The classical synthetic protocols for the above quinoline intermediates and natural products suffer from some disadvantages such as low yield,[15] lack of easy availability/ preparation of the reagent,[16-18] prolonged reaction time, multiple steps, requirement of excess of reagents/catalysts, need for special apparatus and harsh reaction conditions.[16,17] In this connection and by knowing the advantages of microwave reactions,[19-21] we felt that the synthesis of the above intermediates and quinoline alkaloids using microwave irradiation in an unaltered domestic microwave oven would make the task much easier than the thermal synthesis. Hence we wish to report a convenient and efficient synthesis of 4-hydroxy-2-quinolinone and 4-methoxy-1-methyl-2-quinolinone derivatives under microwave irradiation.

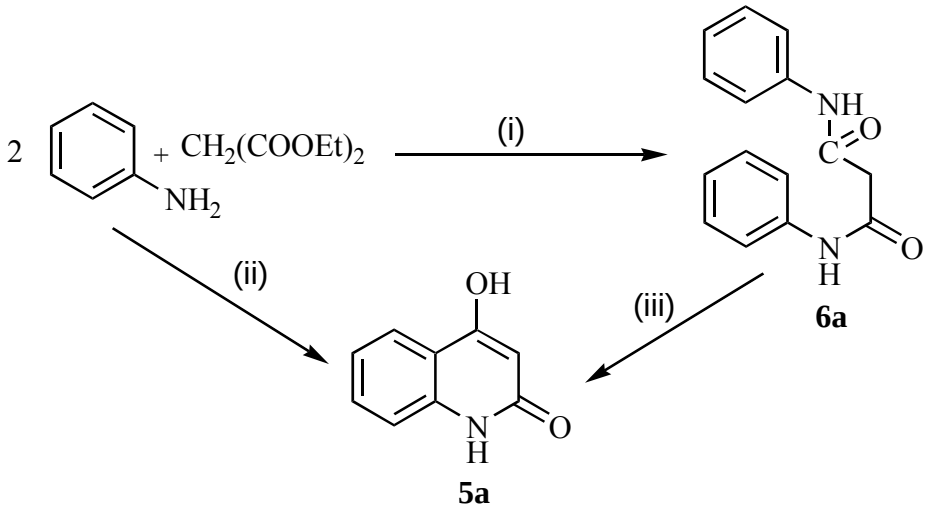
Results and Discussion

In an initial study, a mixture of aniline and diethylmalonate (2:1 molar ratio) was taken in a beaker (without adding any support, i.e., neat conditions), and irradiated under microwaves. This type of reaction is expected to be the most economical method since neither catalyst nor solvent is used. We failed to obtain 4-hydroxy-2-quinolinone (**5a)**; but the *N*,*N'*-diphenyl malonamide (**6a**) was formed in 20 min (90% yield) (Scheme 2). This result agreed with the report given by Lange *et al*[22] in their synthesis of 3-phenyl substituted 4-hydroxy-2-quinolinones. By contrast, in the presence of a catalytic amount of *p*-toluenesulfonic acid, the quinolinone **5a** was isolated in 89% yield in 6 min under the same reaction conditions (Scheme 2). IR spectrum of **5a** exhibited the absorption bands at 1660, 1606 cm^{-1} ascribable to carbonyl groups and a broad NH absorption in the region 3400-2900 cm^{-1}. The ^{1}H-NMR spectrum represented a singlet at δ 5.80 for the C_3-proton, a multiplet in the region δ 7.05-7.65 for aromatic protons and a doublet at δ 7.70 for C_5-proton. The singlet at δ 10.35 is accounted for NH proton and a broad singlet at δ 10.55 is due to the –OH group.

Table 1. Effect of solid support for the synthesis of **5a** under microwave irradiation (Power = 320W)

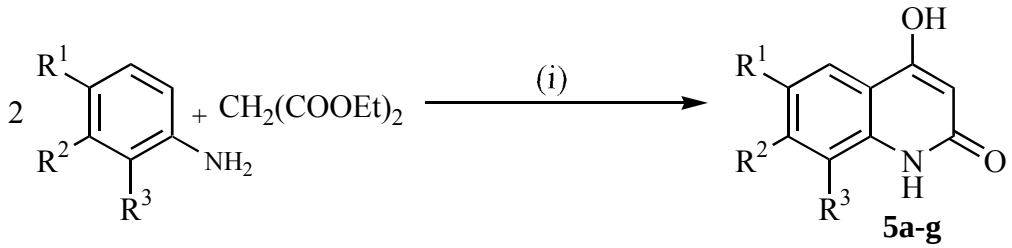
Support	Time (min)	Yield (%)
No	20	-
Silica gel	12	55
Acidic alumina	12	46
K_{10} clay	12	41
p-Toluenesulfonic acid	6	89

Different solid supports, including silica gel, acidic alumina and montmorillonite (K_{10} clay) were also checked to define the most effective catalyst (Table 1). From these results, it is obvious that *p*-toluenesulfonic acid is the most adaptable and simplest catalyst for the synthesis of **5a**, as work-up is simply reduced to treatment with ice-cold water. Thus, we have extended these conditions to the synthesis of various 4-hydroxy-2-quinolinones (**5a-g**) with high yields (Scheme 3; Table 2). It was also attempted to convert N,N'-diphenyl malonamide (**6a**) to 4-hydroxy-2-quinolinone (**5a**) by microwave irradiation, in which the reaction was (Scheme 2) completed with in 3 min, in presence of the catalyst *p*-toluenesulfonic acid.



(i) neat condition, mw, 20 min (ii) *p*-toluenesulfonic acid, mw, 6 min
(iii) *p*-toluenesulfonic acid, mw, 3 min

Scheme 2



(i) *p*-toluenesulfonic acid, mw, 6-11 min

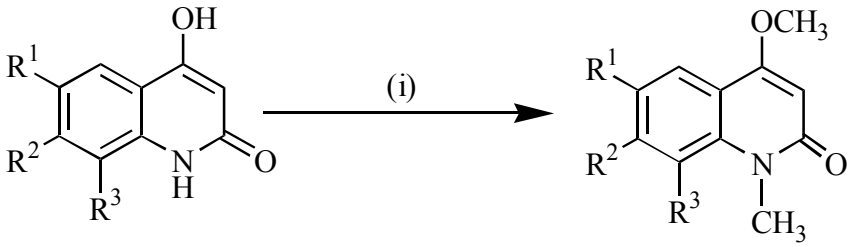
Scheme 3

Table 2. Microwave Synthesis of 4-Hydroxy-2-quinolinones under the catalyst *p*-toluenesulfonic acid

Compound	R^1	R^2	R^3	Reaction Time (min)	Yield (%)	mp (˚C)	Lit. mp (˚C)
5a	H	H	H	6	89	>300	>300[23]
5b	H	H	OCH_3	6	90	248	245-248[23]
5c	OCH_3	H	H	8	89	300	298-300[23]
5d	H	OCH_3	OCH_3	10	85	246	244-246[13]
5e	OCH_3	H	OCH_3	11	84	290	288-291[16]
5f	H	H	CH_3	7	92	>300	360[18]
5g	CH_3	H	H	8	96	>300	>300[24]

Reaction of 4-hydroxy-8-methyl-2-quinolinone (**5f**) with dimethyl sulfate, *N*,*N*-dimethylformamide and potassium carbonate under microwave irradiation afforded methylated quinolinone **8** in 70% yeild in 3 min (Scheme 4). The formation of 1,8-dimethyl-4-methoxy-2-quinolinone (**8**) is supported by the observation of peak in the expected chemical shifts of –OCH_3 and N-CH_3 protons as singlets at δ 3.99 and 3.81 respectively in the ^{1}H-NMR spectrum. Similar reaction of **5e** and **5g** with the same reagents yielded 4,6,8-trimethoxy-1-methyl-2-quinolinone (**7**) and 1,6-dimethyl-4-methoxy-2-quinolinone (**9**) in good yield.

The synthesis of natural products demonstrates an interesting application of this synthetic methodology. Treatment of 4-hydroxy-2-quinolinone (**5a**) with *N*,*N*-dimethylformamide, dimethyl sulfate and potassium carbonate gave 4-methoxy-1-methyl-2-quinolinone (**1**) in 66% yield in 3 min. Similarly, treatment of **5b-d** with the above reagents afforded the natural products **2, 3,** and **4** in good yield. The spectroscopic properties of our synthetic materials **1** to **4** agreed well with those reported in the literature.[10-13] In addition to its simple reaction conditions, this procedure has the advantage of very short reaction times, easy experimental and work-up procedures.



5a-g **1-4 & 7-9**

(i) DMF, dimethyl sulfate, K_2CO_3, mw, 3-6 min

Scheme 4

Conclusions

In conclusion, we have demonstrated an efficient, mild method for the synthesis of 4-hydroxy-2-quinolinones and in parallel, we have also developed an easy and fast synthetic methodology for naturally occurring 4-methoxy-1-methyl-2-quinolinone derivatives.

Table 3. Microwave Synthesis of 4-Methoxy-1-methyl-2-quinolinones

Compound	R^1	R^2	R^3	Reaction Time (min)	Yield (%)	mp (˚C)	Lit. mp (˚C)
1	H	H	H	3	66	100	100-101[10]
2	H	H	OCH_3	3	69	140	139-140[11]
3	OCH_3	H	H	4	70	148	145-146[12]
4	H	OCH_3	OCH_3	5	65	146	143-148[13]
7	OCH_3	H	OCH_3	6	67	163	161-162[16]
8	H	H	CH_3	3	70	236	-
9	CH_3	H	H	4	69	241	-

Experimental Section

General Procedures. Melting points were recorded on Boetieus microheating table and are uncorrected. IR (KBr) spectra were recorded on a Shimadzu-8201 FT spectrophotometer. ^{1}H-NMR spectra were recorded on AMX-400 (400MHz) spectrophotometer, using TMS as an internal reference, and Mass spectra were recorded at 70eV on a Joel JMS-D-300 instrument. The reactions were carried out in a domestic microwave oven (KENSTAR –OM-20ESP, 2450 MHz).

General procedure for the synthesis of 4-hydroxy-2-quinolinones (5a-g). Respective aniline (10 mmol), diethyl malonate (5 mmol) and *p*-toluenesulfonic acid (120mg) were taken in a 50 ml beaker and properly mixed with the help of a glass rod. The so-obtained paste was irradiated in a microwave oven at the power of 320 W for the specified time (**Table 2**). After irradiation, cold water was added to the reaction mixture. The solid obtained was filtered, washed with water, dried and recrystallised (Ethanol-Acetic acid) to afford the desired product in good yield.

4-Hydroxy-2-quinolinone (5a). υ_{max} (KBr)/cm^{-1}: 3400-2900, 1660, 1606, 1514; ^{1}H-NMR (DMSO-d_6) δ (ppm): 5.80 (s, 1H, C_3-H), 7.05-7.65 (m, 3H, Ar-H), 7.70 (d, 1H, C_5-H), 10.35 (s, 1H, NH), 10.55 (brs, 1H, OH); MS (m/z): 161 ($M^{+\cdot}$). Anal. Found. C 67.05; H 4.40; N 8.68. Calcd. For $C_9H_7NO_2$; C 67.08; H 4.38; N 8.69.

4-Hydroxy-8-methoxy-2-quinolinone (5b). υ_{max} (KBr)/cm^{-1}: 3400-2900, 1661, 1605, 1514; ^{1}H-NMR (DMSO-d_6) δ (ppm): 3.90 (s, 3H, C_8-OCH_3), 5.86 (s, 1H, C_3-H), 7.14-7.40, (m, 2H, C_6-H & C_7-H), 7.78 (d, 1H, C_5-H), 10.32 (s, 1H, NH), 10.54 (brs, 1H, OH); MS (m/z): 191 ($M^{+\cdot}$). Anal. Found. C, 62.79; H, 4.76; N, 7.30. Calcd. For $C_{10}H_9NO_3$; C 62.82; H 4.75; N 7.33.

4-Hydroxy-6-methoxy-2-quinolinone (5c). υ_{max} (KBr)/cm^{-1}: 3450-2950, 1660, 1606, 1515; ^{1}H-NMR (DMSO-d_6) δ (ppm): 3.91 (s, 3H, C_6-OCH_3), 5.90 (s, 1H, C_3-H), 7.21-7.54, (2d, 2H, C_7-H & C_8-H), 7.81 (s, 1H, C_5-H), 10.34 (s, 1H, NH), 10.53 (brs, 1H, OH); MS (m/z): 191 ($M^{+\cdot}$). Anal. Found. C 62.83; H 4.78; N 7.35. Calcd. For $C_{10}H_9NO_3$; C 62.82; H 4.75; N 7.33.

7,8-Dimethoxy-4-hydroxy-2-quinolinone (5d). υ_{max} (KBr)/cm^{-1}: 3390-2900, 1660, 1606, 1515; ^{1}H-NMR (DMSO-d_6) δ (ppm): 3.80 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 6.03 (s, 1H, C_3-H), 7.08-7.62 (2d, 2H, C_5-H & C_6-H), 10.35 (s, 1H, NH), 10.55 (brs, 1H, OH); MS (m/z): 221 ($M^{+\cdot}$). Anal. Found. C 59.75; H 5.05; N 6.30. Calcd. For $C_{11}H_{11}NO_4$; C 59.72; H 5.02; N 6.33.

6,8-Dimethoxy-4-hydroxy-2-quinolinone (5e). υ_{max} (KBr)/cm^{-1}: 3400-2900, 1661, 1606, 1513 ; ^{1}H-NMR (DMSO-d_6) δ (ppm): 3.52 (s, 3H, OCH_3), 3.62 (s, 3H, OCH_3), 6.27 (s, 1H, C_3-H), 7.58 (s, 1H, C_7-H), 7.62 (s, 1H, C_5-H), 10.33 (s, 1H, NH), 10.54 (brs, 1H, OH); MS (m/z): 221 ($M^{+\cdot}$). Anal. Found. C 59.71; H 5.00; N 6.31. Calcd. For $C_{11}H_{11}NO_4$; C 59.72; H 5.02; N 6.33.

4-Hydroxy-8-methyl-2-quinolinone (5f). υ_{max} (KBr)/cm^{-1}: 3390-2900, 1661, 1605, 1515; ^{1}H-NMR (DMSO-d_6) δ (ppm): 2.40 (s, 3H, C_8-CH_3), 5.78 (s, 1H, C_3-H), 7.06-7.37 (m, 2H, C_6-H & C_7-H), 7.67 (d, 1H, C_5-H), 10.31 (s, 1H, NH), 10.53 (brs, 1H, OH); MS (m/z): 175 ($M^{+\cdot}$). Anal. Found. C 68.58; H 5.15; N 8.09. Calcd. For $C_{10}H_9NO_2$; C 68.57; H 5.18; N 8.00.

4-Hydroxy-6-methyl-2-quinolinone (5g). υ_{max} (KBr)/cm^{-1}: 3400-2900, 1662, 1605, 1515; ^{1}H-NMR (DMSO-d_6) δ (ppm): 2.43 (s, 3H, C_6-CH_3), 5.81 (s, 1H, C_3-H), 7.10-7.40, (2d, 2H, C_7-H & C_8-H), 7.68 (s, 1H, C_5-H), 10.33 (s, 1H, NH), 10.54 (brs, 1H, OH); MS (m/z): 175 ($M^{+\cdot}$). Anal. Found. C 68.52; H 5.17; N 8.00. Calcd. For $C_{10}H_9NO_2$; C 68.57; H 5.18; N 8.00.

Synthesis of 4-methoxy-1-methyl-2-quinolinones (3a-g). Respective 4-hydroxy-2-quinolinone (1 mmol) was taken in 100 ml conical flask and to this, dimethyl sulfate (2 mmol), potassium carbonate (0.8 g) and N, N-dimethyl formamide (5 ml) were added, mixed well and irradiated for the specified time (**Table 3**). The reaction was monitored for every 30 seconds by the tlc. After irradiation, the reaction mixture was poured into ice water and extracted well with chloroform. The extract was dried (Na_2SO_4) and column chromatographed to yield the pure compound. The

spectroscopic properties of our synthetic materials **1** to **4** and **7** agreed well with those reported in the literature[10-13].

1,8-Dimethyl-4-methoxy-2-quinolinone (8). υ_{max} (KBr)/cm^{-1}: 1642, 1580, 1459; ^{1}H-NMR (DMSO-d_6) δ (ppm): 2.40 (s, 3H, C_8-CH_3), 3.75 (s, 3H, -NCH_3), 3.95 (s, 3H,-OCH_3), 6.01 (s, 1H, C_3-H), 7.06-7.68 (m, 2H, C_6-H & C_7-H), 8.01 (d, 1H, C_5-H); MS (m/z): 203 ($M^{+\cdot}$). Anal. Found. C 70.85; H 6.46; N 6.86. Calcd. For $C_{12}H_{13}NO_2$; C 70.93; H 6.45; N 6.89.

1,6-Dimethyl-4-methoxy-2-quinolinone (9). υ_{max} (KBr)/cm^{-1}: 1643, 1580, 1460; ^{1}H-NMR (DMSO-d_6) δ (ppm): 2.42 (s, 3H, C_6-CH_3), 3.81 (s, 3H, -NCH_3), 3.99 (s, 3H, -OCH_3), 6.02 (s, 1H, C_3-H), 7.20 – 7.62 (2d, 2H, C_7-H & C_8-H), 7.99 (s, 1H, C_5-H); MS (m/z): 203 ($M^{+\cdot}$). Anal. Found. C 70.91; H 6.49; N 6.89. Calcd. For $C_{12}H_{13}NO_2$; C 70.93; H 6.45; N 6.89.

Acknowledgments

The authors thank Sophisticated Instruments Facility, Indian Institute of Science, Bangalore, for recording ^{1}H-NMR spectra.

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