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Research Article

MICROWAVE-ASSISTED SYNTHESIS OF SOME QUINOLINE ALKALOIDS: *MONTONINE*, 4-METHOXYQUINOLINE-2(1*H*)-ONE AND ITS ANALOGUES

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ABSTRACT

The microwave synthesis of quinoline alkaloid *montonine* **2a** and its analogues **2b-e** was achieved in 6-8 min by methoxydechlorination of 2,4-dichloroquinolines **1a-e** using TBAB as phase transfer catalyst. Selective hydrolysis of **2a-e** by sodium acetate/acetic acid afforded 4-methoxyquinolin-2(1*H*)-one **3a** and its derivatives including natural alkaloid *edulitine*.

Keywords: Edulitine, Quinolines, Alkaloids, Phase transfer catalyst, Microwave.

INTRODUCTION

A considerable number of medicinally important quinoline alkaloids have been isolated from the *Rutaceae* family of plants.[1] Representative examples of some simple quinoline alkaloids include 2,4-dimethoxyquinoline, 4-methoxyquinolin-2(1*H*)-one and edulitine. These compound's plant sources have been shown to exhibit a variety of biological properties including antibacterial,[2] antifungal,[3] antiviral,[4] anti-protozoal[5] and anti-platelet aggregation [6] activities. Also these compounds are found to be key intermediates in the synthesis of several furoquinoline and pyranoquinoline type heterocycles[7-9]. Dictamine group of alkaloids were efficiently prepared[10] from 2,4-dimethoxyquinolines by organolithiation and wittig reaction. Recently, 4-methoxyquinolin-2(1*H*)-one was used for the synthesis of atanine[11] and anticancerous indolo[2,3-*b*]quinoline derivatives[12].

In recent years, there is an increasing interest in the use of microwave-induced rate acceleration technology[13-16] in organic synthesis in view of the mild, clean, convenient, greater selectivity, easier workup, spontaneity of the reaction process in comparison to the conventional solution phase reactions and the associated ease of manipulation. It is of note that this technique offers an environmentally friendly process of organic synthesis[17,18].

Phase Transfer Catalysis (PTC) a condition[19,20] in the absence of organic solvent offers an improved technique, under which several organic syntheses were achieved. Hence, by coupling microwave technology and solvent-free solid-liquid PTC conditions have become an efficient methodology to carry out organic reactions with substantial improvements in terms of reaction conditions and simplicity in operating procedures. Herein we report a new and efficient microwave-assisted solvent-free synthesis of 2,4-dimethoxyquinolines and 4-methoxyquinolin-2(1*H*)-ones under PTC condition.

MATERIALS AND METHOD

Melting points (mp) were determined using Boetieus micro heating table and are uncorrected. IR (KBr, cm^{-1}) spectra were obtained on Shimadzu-8201 spectrophotometer. ^1H NMR spectra were recorded on Bruker AMX-400 (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 synthesis of 2, 4-dimethoxyquinolines (2a-e)

2,4-Dichloroquinoline **1a-e** (1 mmol), tetrabutyl ammonium bromide (TBAB, 200 mg), sodium methoxide (108 mg) and few drops of water were mixed well and irradiated at 160 W under microwave condition for the specified time (**Table 1**). After completion of the reaction, the mixture was poured into ice, the formed precipitate was filtered, washed with sufficient water and then recrystalised from hexane-ethyl acetate.

2,4-dimethoxyquinoline (2a): IR (KBr**)**: ν=1622, 1580 cm^{-1}; ^1H NMR (DMSO-d_6): δ=7.98 (d, ^3J (H,H) = 8.3 Hz, 1H; C_5-H), 7.71 (d, 1H; C_8-H), 7.63 (t, 1H; C_7-H), 7.37 (t, 1H; C_6-H), 6.45 (s, 1H; C_3-H), 3.99 (s, 3H; C_2-OCH_3), 3.94 (s, 3H; C_4-OCH_3); ^{13}C NMR (DMSO-d_6): δ=163.9, 163.4, 147.1, 130.0, 126.9, 123.3, 121.8, 119.0, 90.7, 55.7, 53.4. MS *m/z*: 189 (100 %, M^+) 188 (93%, M^+-H).

6-Methyl-2,4-dimethoxyquinoline (2b): IR (KBr**)**: ν=1625, 1580 cm^{-1}; ^1H NMR (DMSO-d_6): δ=8.04 (s, 1H; C_5-H), 7.78 (d, 1H; C_8-H), 7.60 (d, 1H; C_7-H), 6.38 (s, 1H; C_3-H), 4.02 (s, 3H; C_2-OCH_3), 3.95 (s, 3H; C_4-OCH_3), 2.47 (s, 3H; C_6-CH_3); MS *m/z*: 203 (100 %, M^+).

8-Methyl-2,4-dimethoxyquinoline (2c): IR (KBr**)**: ν=1620, 1585 cm^{-1}; ^1H NMR (DMSO-d_6): δ=7.93 (d, *J* = 8.2 Hz, 1H; C_5-H), 7.64 (d, 1H; C_7-H), 7.45 (t, 1H; C_6-H), 6.41 (s, 1H; C_3-H), 4.05 (s, 3H; C_2-OCH_3), 4.00 (s, 3H; C_4-OCH_3), 2.60 (s, 3H; C_8-CH_3); MS *m/z*: 203 (100 %, M^+).

6-Methoxy-2,4-dimethoxyquinoline (2d): IR (KBr**)**: ν=1620, 1578 cm^{-1}; ^1H NMR (DMSO-d_6): δ=7.52 (s, 1H; C_5-H), 7.25 (d, 1H; C_8-H), 7.13 (d; 1H, C_7-H), 6.45 (s, 1H; C_3-H), 4.01 (s, 3H; C_2-OCH_3), 3.96 (s, 3H; C_4-OCH_3), 3.92 (s, 3H; C_6-OCH_3); MS *m/z*: 219 (100 %, M^+).

8-Methoxy-2,4-dimethoxyquinoline (2e): IR (KBr**)**: ν=1625, 1580 cm^{-1}; ^1H NMR (DMSO-d_6): δ=7.54 (d, *J* = 8.2 Hz, 1H; C_5-H), 7.27 (t, 1H; C_6-H), 7.14 (d, 1H; C_7-H), 6.46 (s, 1H; C_3-H), 3.97 (s, 3H; C_2-OCH_3), 3.94 (s, 3H; C_4-OCH_3), 3.90 (s, 3H; C_8-OCH_3); ^{13}C NMR (DMSO-d_6): δ=164.1, 163.8, 150.1, 149.2, 132.2, 123.6, 121.8, 119.4, 91.2, 55.6, 54.5, 53.7; MS *m/z*: 219 (100 %, M^+).

General procedure for the synthesis of 4-methoxyquinolin-2(1*H*)-ones (3a-e)

2,4-Dimethoxyquinoline (1 mmol) acetic acid (10 mL) and sodium acetate (8 g) were heated in a microwave oven at 160 W for the specified time (**Table 2**). After the reaction, the mixture was added to ice. The precipitated solid was filtered, dried and recrystalised from ethyl acetate.

4-Methoxyquinolin-2(1*H*)-one (3a): IR (KBr**)**: ν=3100-3200 (NH), 1668 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6): δ=11.34 (s, 1H; NH), 7.85 (d, *J = 8.1* Hz, 1H; C_5-H), 7.61 (t, 1H; C_7-H), 7.37 (d, 1H; C_8-H), 7.29 (t, 1H; C_6-H), 5.87 (s, 1H; C_3-H), 3.91 (s, 3H; C_4-OCH_3); ^{13}C NMR (DMSO-d_6): δ=166.4, 165.0, 138.7, 131.5, 123.1, 122.4, 115.1, 114.6, 96.2, 55.5; MS *m/z*: 175 (100 %, M^+), 132 (63%, M^+-CONH).

6-Methyl-4-methoxyquinolin-2(1*H*)-one (3b): IR (KBr**)**: ν=3150-3310 (NH), 1664 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6): δ=10.35 (s, 1H; NH), 7.90 (s, 1H; C_5-H), 7.52 (d, 1H; C_8-H), 7.32 (d, 1H; C_7-H), 6.01 (s, 1H; C_3-H), 3.93 (s, 3H; C_4-OCH_3), 2.52 (s, 3H; C_6-CH_3); MS *m/z*: 189 (100 %, M^+).

8-Methyl-4-methoxyquinolin-2(1*H*)-one (3c): IR (KBr**):** ν=3200-3300 (NH), 1665 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6): δ=10.46 (s, 1H, NH), 7.83 (d, *J* = 8.2 Hz, 1H; C_5-H), 7.63 (d, 1H; C_7-H), 7.31 (t, 1H; C_6-H), 6.03 (s, 1H; C_3-H), 3.92 (s, 3H; C_4-OCH_3), 2.49 (s, 3H; C_8-CH_3); MS *m/z*: 189 (100 %, M^+).

6-Methoxy-4-methoxyquinolin-2(1*H*)-one (3d): IR (KBr**):** ν=3200-3300 (NH), 1662 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6): δ=10.72 (s, 1H; NH), 7.58 (s, 1H; C_5-H), 7.52 (d, 1H; C_8-H), 7.15 (d, 1H; C_7-H), 5.88 (s, 1H; C_3-H), 3.90 (s, 3H; C_6-OCH_3), 3.94 (s, 3H; C_4-OCH_3); MS *m/z*: 205 (100 %, M^+).

8-Methoxy-4-methoxyquinolin-2(1*H*)-one (3e): IR (KBr**):** ν=3210-3300 (NH), 1668 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6): δ=10.35 (s, 1H; NH), 7.35 (d, *J = 8.1 Hz*, 1H; C_5-H), 7.08-7.15 (m, 2H; C_6-H & C_7-H), 5.89 (s, 1H; C_3-H), 3.90 (s, 3H; C_4-OCH_3), 3.87 (s, 3H; C_8-OCH_3); ^{13}C NMR (DMSO-d_6): δ=166.5, 164.8, 149.8, 139.2, 132.3, 123.4, 115.2, 114.7, 96.5, 55.7, 54.3; MS *m/z*: 205 (100 %, M^+).

Table 1: Physical data of Compound 2a-e & 3a-e

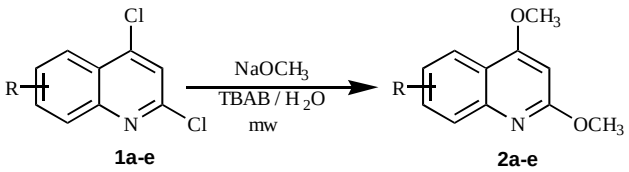
Compound	Reaction Time (min)	Yield (%)	mp °C	Compound	Reaction Time (min)	Yield (%)	mp °C
2a	6	92	79-80	**3a**	5	91	248-249
2b	7	91	55-56	**3b**	4	94	235-237
2c	8	90	45-47	**3c**	5	89	248-249
2d	4	86	78-80	**3d**	6	90	220-223
2e	8	87	152-154	**3e**	6	82	240-242

RESULTS AND DISCUSSION

2,4-Dimethoxyquinoline **2a** is the proposed structure for montanine, isolated from *Ruta Montana*[21] Before its isolation as natural product, the synthesis was reported. The synthetic method generally involves O-O-dialkylation of 4-hydroxyquinolin-2(1*H*)-one using diazomethane in methanol[22] or methyl iodide, dimethyl sulphate and potassium hydroxide in acetone[23]. Recent report of the synthesis of 2,4-dimethoxyquinolines from 4-hydroxy quinolin-2(1*H*)-ones involves treatment with methyl iodide in presence of $AgCO_3$ as catalyst under Argon atmosphere for 3 days.

In another methodology, 2,4-dimethoxyquinolines were obtained[16] by treating 2,4-dichloroquinolines with sodium methoxide in refluxing methanol for 20-25 hr. The process is slow; the overall yield of the transformation was only about 45% and shorter reaction times led to isolation of 2-methoxy-4-haloquinolines along with **2a**.

Our preliminary reaction centered on the methoxylation of 2,4-dichloroquinolines 1. When 1a was irradiated with sodium methoxide in methanol for 20 min at 160 W under microwave, mixture of products was recovered. Substitution at C-2 position is known to be kinetically favored and the second substitution is slowed considerably by the methoxy group at C-2 making bi-substitution difficult to drive the reaction to completion. Therefore, the same reaction was then tried out in solid sodium methoxide, Phase Transfer Catalyst (PTC) such as Tetra Butyl Ammonium Bromide (TBAB) and water under microwave condition. Gratifyingly, this reaction led to methoxylation of 1a and gave 2,4-dimethoxyquinoline 2a as the exclusive product in 92% yield (mp. 79-80°C; Lit. mp. 80-81°C) (Scheme 1). The use of phase transfer catalyst reduced the reaction time from 25 hr to just 6 min, and application of this methodology is further proved by the synthesis of derivatives of 2,4-dimethoxyquinoline in very good yield (Scheme 1; Table 1).



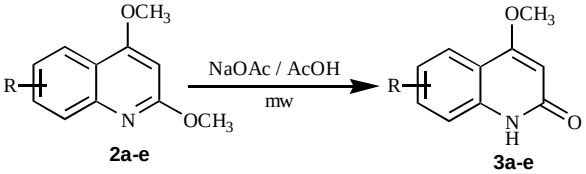
1a-e **2a-e**

1a, 2a R = H; **1b, 2b** R = 6-CH_3; **1c, 2c** R = 8-CH_3; **1d, 2d** R = 6-OCH_3; **1e, 2e** R = 8-OCH_3

Scheme 1

4-Methoxyquinolin-2(1*H*)-one and related compounds like edulitine are natural alkaloids found rich in *Zanthoxylum* species. Generally 4-methoxyquinolin-2(1*H*)-one is obtained from 2,4-dimethoxyquinoline by refluxing with hydrochloric acid[7a] or aceticacid. Recently,[7e] 4-methoxyquinolin-2(1*H*)-one was obtained from 2,4-dimethoxyquinoline using HBr, THF/H_2O in 54% yield. In another report,[8] **3a** was prepared from 4-hydroxyquinolin-2(1*H*)-one by selective methylation using dimethyl sulphate, K_2CO_3 and acetone. These processes suffer some disadvantages like longer reaction time, poor yield and use of hazardous chemicals. Here we thought of applying simple and solvent-free methodology for the synthesis of 4-methoxyquinolin-2(1*H*)-ones.

Thus, 2,4-dimethoxyquinoline **2a** was treated with 1 equivalent mixture of sodium acetate and acetic acid under microwave, which gave mixture of starting compounds and product. A range of conditions was investigated by changing the molar ratio of sodium acetate and acetic acid, in which 2 equivalent of sodium acetate and acetic acid successfully gave **3a** in 90% yield (**Scheme 2**). The structure of the **3a** was assigned on the basis of reported [8] spectral (IR, ^1H NMR ^{13}C NMR, Mass) and analytical (mp, mmp, CHN) data. Application of this methodology is further proved by the synthesis of derivatives of 4-methoxyquinolin-2(1*H*)-one (**3a-e**) in very good yield (**Scheme 2; Table 1**).



2a-e **3a-e**

2a, 3a R = H; **2b, 3b** R = 6-CH_3; **2c, 3c** R = 8-CH_3; **2d, 3d** R = 6-OCH_3; **2e, 3e** R = 8-OCH_3

Scheme 2

Microwave-assisted synthesis of some quinoline alkaloids: *Montonine*, 4-methoyquinolin-2(1*H*)-one and its analogues

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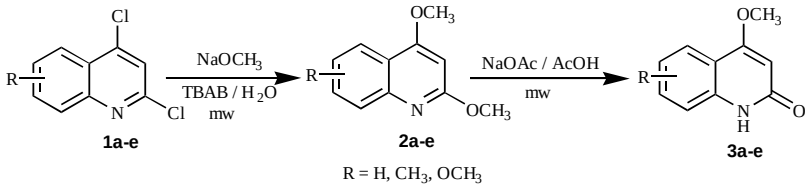
The microwave synthesis of quinoline alkaloid montonine **2a** and its analogues 2b-e was achieved by methoxydechlorination of 2,4-dichloroquinolines **1a-e** using TBAB as phase transfer catalyst.



Graphical Abstract

CONCLUSION

In conclusion, the PTC catalysed methoxylation reaction of 2,4-dichloroquinolines entails an efficient, very easy and solventless method for the synthesis of 2,4-dimethoxyquinolines, in very short reaction time, followed by demethoxylation which gave natural quinoline alkaloids like 4-methoxyquinolin-2(1*H*)-one, edulitine, and their synthetic analogs in good yields. The notable advantages of these procedure are: a) operational simplicity; b) faster reaction; c) high yield and purity of the product and d) avoid the usage of solvents. We believe this will provide a better and more practical alternative to the existing methodologies for the synthesis of the above alkaloids.

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