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Synthesis of some quinoline intermediates under phase transfer catalyst

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ABSTRACT

The microwave synthesis of quinoline alkaloid 4-methoxyquinolin-2(1*H*)-one 3a and its analogues 3b-e was achieved in 8-11 minutes by methoxydechlorinated of 4-chloroquinolin-2(1*H*)-ones 2a-e using TBAB as phase transfer catalyst. The starting compound obtained by selective decholorination of 1a-e by sodium acetate/acetic acid and the structure of synthesized compound has been established by IR, ^{1}H-NMR and Mass spectral data.

Key words: quinoline, alkaloids, acetic acid, phase tranfer cataylst, microwave.

INTRODUCTION

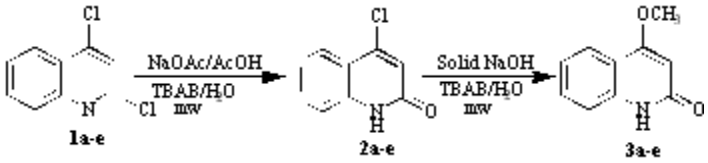
A considerable number of medicinally important quinoline alkaloids have been isolated from the *Rutaceae* family of plants[1]. Representative examples of some simple quinoline alkaloids include 4-methoxyquinolin-2(1*H*)-one and edulitine. These compound's plant sources have been shown to exhibit a variety 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]. Recently, 4-methoxyquinolin-2(1*H*)-one was used for the synthesis of atanine[8] and anticancerous indolo[2,3-*b*]quinoline derivatives).

Generally 4-methoxyquinolin-2(1*H*)-one is obtained from 2,4-dimethoxy quinoline by refluxing with hydrochloric acid or HBr, THF/H_2O in 54% yield[7,8]. In another report, 3a was prepared from 4-hydroxyquinolin-2(1*H*)-one by selective methylation using dimethyl sulphate, K_2CO_3 and acetone[9]. These processes suffer some disadvantages like longer reaction time, poor yield and use of hazardous chemicals.

In recent years, there is an increasing interest in the use of microwave-induced rate acceleration technology[10, 11] 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[12-14].

Phase Transfer Catalysis (PTC) conditions[15,16] in the absence of organic solvent offer 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 solvent-free synthesis of 4-methoxyquinolin-2(1*H*)-ones from 4-chloroquinolin-2(1*H*)-ones and under PTC condition. (Scheme 1)



Scheme 1:

MATERIAL AND METHODS

Melting points were determined using Boetieus micro heating table and are uncorrected. IR (KBr, cm^{-1}) spectra were obtained on Shimadzu–8201 spectrometer. ^{1}H-NMR and ^{13}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 synthesis of 4-chloroquinolin-2(1*H*)-ones (4a-e)

A mixture of 2,4-dichloroquinoline (1 mmol), sodium acetate (8 g) and acetic acid (10 mL) and tetrabutyl ammonium bromide (100 mg) was irradiated in a microwave oven at 160 W for the specified time (**Table 1**). After completion of the reaction, the mixture was poured into ice, the resulting white precipitate was filtered off and recrystalised from dilute acetic acid.

4-Chloroquinolin-2(1*H*)-one (2a)

IR (KBr, cm^{-1}): 3200-3400, 1664. ^{1}H NMR (DMSO), δ_H 11.20 (s, 1H, NH), 7.99 (d, 1H, C_5-H), 7.59 (t, 1H, C_7-H), 7.28-7.37 (m, 2H, C_6-H & C_8-H), 6.88 (s, 1H, C_3-H). ^{13}C NMR (DMSO), d_C 166.5, 147.2, 144.4, 130.5, 127.6, 124.8, 124,2, 123.3, 110.5. MS (70eV): *m/z* 179 (100 %, $M^{+\cdot}$), 181 (33%, $M^{+\cdot}$+2), 151, 144, 116.

6-Methyl-4-chloroquinolin-2(1*H*)-one (2b)

IR (KBr, cm^{-1}): 3150-3300, 1663. ^{1}H NMR (DMSO), δ_H 11.18 (s, 1H, NH), 8.01 (s, 1H, C_5-H), 7.30-7.66 (m, 2H, C_7-H & C_8-H), 6.86 (s, 1H, C_3-H), 2.53 (s, 3H, C_6-CH_3. MS (70eV): *m/z* 193 (100 %, M^+), 195 (33%, $M^{+\cdot}$ +2).

8-Methyl-4-chloroquinolin-2(1*H*)-one (2c)

IR (KBr, cm^{-1}): 3200-3350, 1664. ^{1}H NMR (DMSO), δ_H 11.21 (s, 1H, NH), 7.98 (d, 1H, C_5-H), 7.32-7.62 (m, 2H, C_6-H & C_7-H), 6.87 (s, 1H, C_3-H), 2.55 (s, 3H, C_8-CH_3. MS (70eV): *m/z* 193 (100 %, M^+), 195 (33%, $M^{+\cdot}$ +2).

6-Methoxy-4-chloroquinolin-2(1*H*)-one (2d)

IR (KBr, cm^{-1}): 3200-3400, 1664. ^{1}H NMR (DMSO), δ_H 11.20 (s, 1H, NH), 7.97 (s, 1H, C_5-H), 7.30-7.70 (m, 2H, C_7-H & C_8-H), 6.87 (s, 1H, C_3-H), 3.90 (s, 3H, C_6-OCH_3. MS (70eV): *m/z* 209 (100 %, M^+), 211 (33%, $M^{+\cdot}$ +2).

8-Methoxy-4-chloroquinolin-2(1*H*)-one (2e)

IR (KBr, cm^{-1}): 3200-3400, 1663. ^{1}H NMR (DMSO), δ_H 11.18 (s, 1H, NH), 7.99 (d, 1H, C_5-H), 7.30-7.68 (m, 2H, C_6-H & C_7-H), 6.88 (s, 1H, C_3-H), 3.91 (s, 3H, C_8-OCH_3. ^{13}C NMR (DMSO), d_C 166.7, 149.8, 149.3, 145.2, 131.2, 125.2, 124.4, 123.8, 109.3, 55.6. MS (70eV): *m/z* 209 (100 %, M^+), 211 (33%, $M^{+\cdot}$ +2).

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

A mixture of 4-chloroquinolin-2(1*H*)-one (1 mmol), sodium methoxide (108 mg), tetrabutyl

ammonium bromide (100 mg) and 0.5 mL of water was irradiated in a microwave oven for the specified time at 160 W (Table 2). After cooling to room temperature, the solid product formed was collected by filtration, dried and recrystalised from ethyl acetate.

4-Methoxyquinolin-2(1*H*)-one (3a)

IR (KBr, cm^{-1}): 3100-3200, 1668. ^1H NMR (DMSO), δ_H 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_C 166.4, 165.0, 138.7, 131.5, 123.1, 122.4, 115.1, 114.6, 96.2, 55.5. MS (70eV): *m/z* 175 (100 %, M^+), 132 (63%, M^+-CONH).

6-Methyl-4-methoxyquinolin-2(1*H*)-one (3b)

IR (KBr, cm^{-1}) 3150-3310, 1664. ^1H NMR (DMSO), δ_H 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 (70eV): *m/z* 189 (100 %, M^+).

8-Methyl-4-methoxyquinolin-2(1*H*)-one (3c)

IR (KBr, cm^{-1}): 3200-3300, 1665. ^1H NMR (DMSO), δ_H 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 (70eV): *m/z* 189 (100 %, M^+).

6-Methoxy-4-methoxyquinolin-2(1*H*)-one (3d)

IR (KBr, cm^{-1}): 3200-3300, 1662. ^1H NMR (DMSO), d_H 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 (70eV): *m/z* 205 (100 %, M^+).

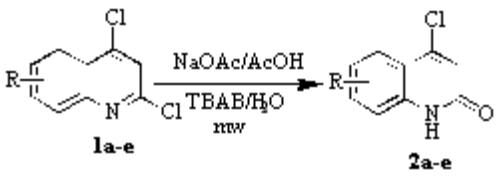
8-Methoxy-4-methoxyquinolin-2(1*H*)-one (3e)

IR (KBr, cm^{-1}): 3210-3300, 1668. ^1H NMR (DMSO), d_H 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_C 166.5, 164.8, 149.8, 139.2, 132.3, 123.4, 115.2, 114.7, 96.5, 55.7, 54.3. MS (70eV): *m/z* 205 (100 %, M^+).

RESULTS AND DISCUSSION

Our preliminary reaction centered on the dechlorination of 2,4-dichloroquinolines 1. When 1a was irradiated with acetic acid (20mL) for 20 min at 160 W under microwave, mixture of products was recovered. Elimination at C-2 position is known to be kinetically favored and the C-4 position is considerably slow process and increase the reaction time 2,4-dihydroxyquinoines obtained. Therefore, the same reaction was then tried out mixture sodium acetate/acetic acid and Phase Transfer Catalyst

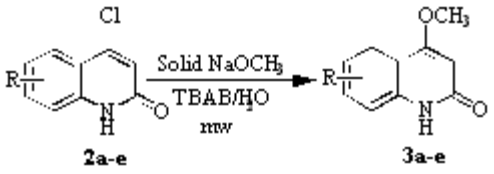
Table 1: Microwave synthesis of 2a-e from 1a-e at 160W



R = H, 6-CH_3,8-CH_3,6-OCH_3,8-OCH_3

Compound	Time (min)	Yield (%)	mp (°C)
2a	8	85	230
2b	11	77	224
2c	11	93	232
2d	9	47	265
2e	11	62	255

Table 2: Microwave synthesis of 3a-e from 2a-e at 160W



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

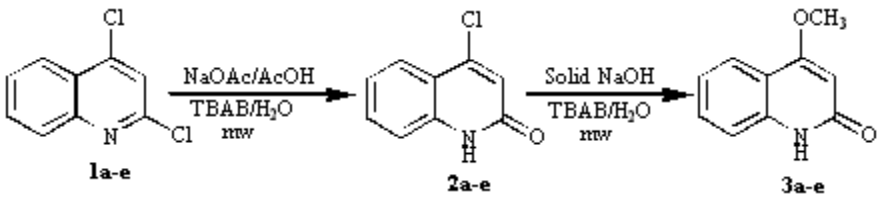
R = H, 6-CH_3,8-CH_3,6-OCH_3,8-OCH_3

Compound	Time (min)	Yield (%)	mp (°C)
3a	5	91	248
3b	4	94	235
3c	5	89	248
3d	6	90	220
3e	6	82	240

(PTC) such as tetrabutyl ammonium bromide (TBAB) and water under microwave condition. Gratifyingly, this reaction led to selective dechlorination of 1a and gave 4-chloro- quinolin-2(1*H*)-one. 2a as the exclusive product in 85% yield (mp. 230°C) (Table 1). The use of phase transfer catalyst reduced the reaction time from hours to min, and application of this methodology is further proved by the synthesis of derivatives of 4-chloroquinolin-2(1*H*)-one in very good yield (Fig 1; Table 1). IR spectrum of the product 2a showed absorptions at 1664 and 3250 cm^{-1} for 2-quinolinone moiety. The ^{1}H-NMR spectrum registered two singlet at d 11.20 and d 6.88 for NH and CH protons, doublet at d 7.99 for C5-H and triplet at d 7.59 for C_7-H and also registered unresolved multiplet at d 7.28-7.37 for C_6 and C_8 protons. The mass spectrum showed a molecular ion peak at *m/z* 179 (100 %, $M^{+\cdot}$) and other peaks at, 181 (33%, $M^{+\cdot}$+2), 151, 144, 116. ^{1}H-NMR and mass spectra also proved 2a as 4-chloroquinolin-2(1*H*)-one. Further, methoxydecholorination of 2a with solid sodium methoxide in presence of TBAB under microwave irradiation for 4 min gave 4-methoxyquinolin-2(1*H*)-one (3a) in 92% yield. (Fig 2; Table 2). All the yields were calculated from crystallized products and the products were identified by comparison of analytical data (mp, mmp, IR, NMR, Mass) with those reported or with authentic samples prepared by the conventional methods. Some new derivatives were also prepared and reported.

Graphical Abstract

Synthesis and Characterization of [1,6]naphthyridin-8-one derivativesThe microwave synthesis of quinoline alkaloid 4-methoxyquinolin-2(1H)-one 3a and its analogues 3b-e was achieved in 8-11 min by methoxydechlorinated of 4-chloroquinolin-2(1H)-ones 2a-e using TBAB as phase transfer catalyst. Vetrivel Nadaraj* and Senniappan Thamarai Selvi.



1a-e **2a-e** **3a-e**

CONCLUSIONS

In conclusion, the PTC catalysed selective decholrination reaction of 2,4-dichloroquinolines entails an efficient, very easy and solventless method for the synthesis of 4-chloroquinolin-2(1*H*)-one, followed by methoxylation gave natural quinoline alkaloids like 4-methoxyquinolin-2(1*H*)-one, edulitine, and their synthetic analogs in good yields and very short reaction time. 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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