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MICROWAVE AND CONVENTIONAL SYNTHESIS OF NOVEL QUINOLINE DERIVATIVES: CLAISEN TYPE REARRANGEMENT

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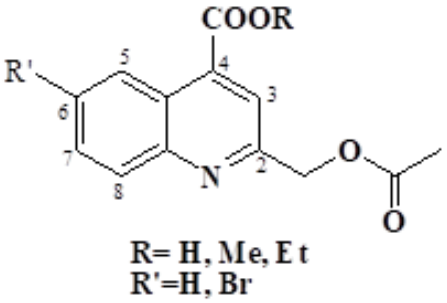
Novel 2-acethoxymethyl quinoline derivatives were synthesized by both conventional and microwave assisted synthesis via corresponding quinoline N-Oxides which undergo Claisen [3,3]-sigmatropic rearrangement, and the resulted products were characterized by spectroscopic techniques. Microwave heating gave good yields and short reaction times compared to conventional heating.



INTRODUCTION

Quinoline derivatives are widely used and intensively studied especially for their biological activities: anti-malarial, anti-inflammatory, analgesic, antifungal, antibacterial, antiviral, anti-arythmic, anticholesterol, anticancer, anticonvulsant, and cardiotonic.[1–10] Other quinoline derivatives are also used as agrochemicals.[11] The antimicrobial activity of certain quinoline N-oxides was already given in the literature.[12–13]

In recent years, application of Microwave in organic synthesis was the subject of several scientific papers in heterocyclic chemistry, medicinal chemistry,[14–17] polymers,[18–19] cycloaddition reactions, the synthesis of radioisotopes,[20] homogeneous and heterogeneous catalysis,[21–23] and green chemistry.[24–25] All these papers agree on the advantages of microwave irradiation, including a clean, cheap, and convenient method; as well as high yields and purity achieved due to heating at high temperatures for a very short time.

In this work we have conducted and achieved the synthesis of novel quinoline derivatives (Fig. 1) using both conventional and microwave assisted synthesis.

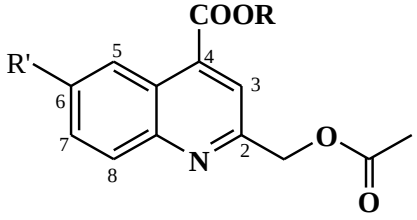


Fig. 1

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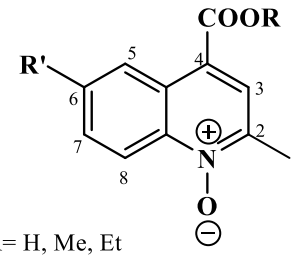
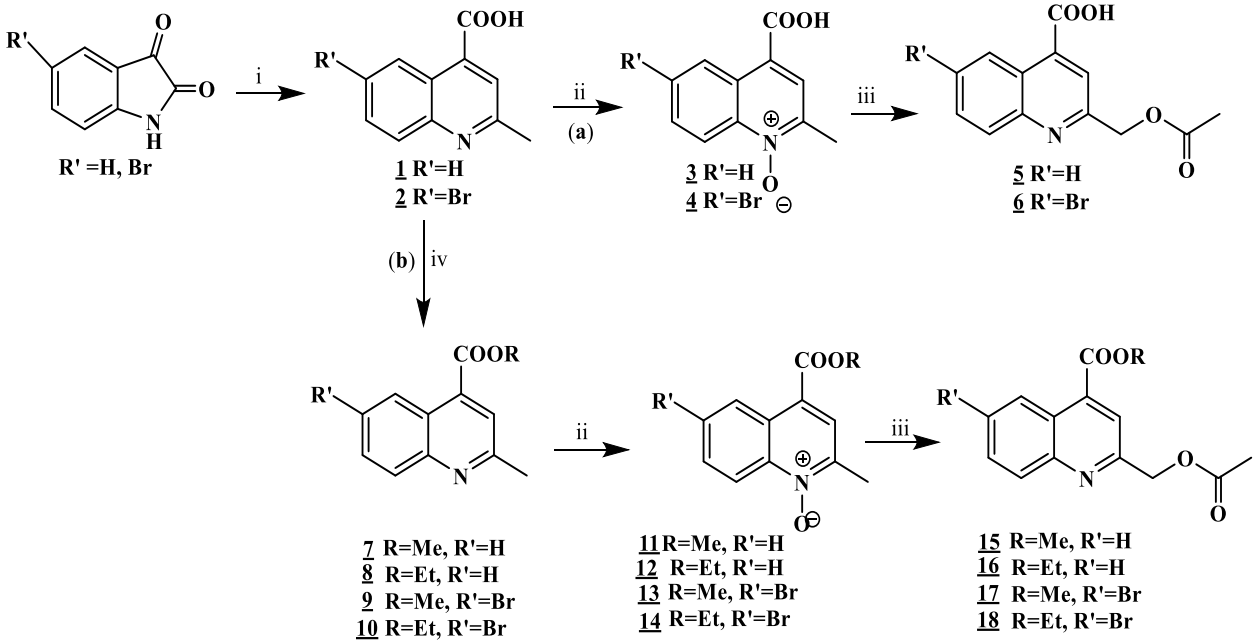
RESULTS AND DISCUSSION

Compounds (**1**) and **(2)** were prepared using isatin and 5-bromoisatin as the starting materials, respectively, and thus via Pfitzinger reaction[26]. Two paths were followed (scheme 1), path (**a**) where (**1**) and **(2)** were directly oxidized and rearranged in the presence of acetic anhydride, and path (**b**) where they were esterified to give the corresponding products (**7)-(10)**. Each of these compounds was then oxidized with hydrogen peroxide (H_2O_2) in glacial acetic acid to yield N-oxide derivatives (Fig 2), which in turn were transformed via a Claisen rearrangement[27] by treatment with acetic anhydride. The final steps, oxidation with H_2O_2 and Claisen rearrangement were performed with both conventional heating and microwave irradiations. These two paths gave, accordingly, six novel 2-acetoxyquinoline derivatives (**5)-(6)** (path **a**) and (**15)-(18)** (path **b**) with good yields. These reactions are depicted in scheme 1.



R= H, Me, Et
R'=H, Br

Fig. 2



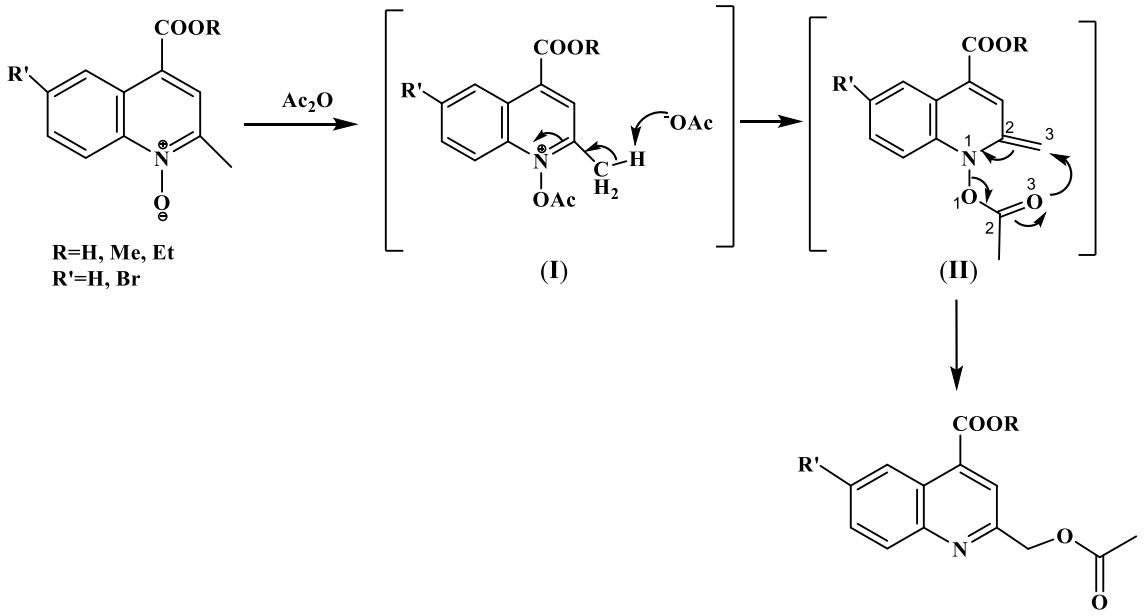
Reagents and conditions: both conventional: (i) KOH, acetone, reflux, 8hrs; (ii) H_2O_2, acetic acid, 65°C, 9h; (iii) acetic anhydride, reflux 4 hrs; (iv) MeOH, H_2SO_4 , reflux 8-19 hrs; Microwave: (ii) H_2O_2, acetic acid, MW, 180 W; (iii) acetic anhydride, MW, 900 W.

Scheme 1

The mechanism of Claisen [3,3]-sigmatropic rearrangement is shown in scheme 2. The scheme shows the passage by two intermediates (**I**) and (**II**). Intermediate (**I**) results from the nucleophilic attack of acetic anhydride by the charged oxygen of the oxide. The methyl group of (**I**) is then deprotonated leading to adduct (**II**), suitable for a Claisen rearrangement to give the final compounds.

Microwave irradiations improved the yields and reaction times immensely. Indeed, N-oxide compounds (**3)-(4)** and (**11)-(14)** were synthesized by conventional heating (at 65°C) after 9 to 11 hours in 38 to 67% yield, and were obtained by microwave (at 100 W) after 30 to 40 minutes in 57 to 84% yield.

2-acetoxyquinoline derivatives (**5)-(6)** and (**15)-(18)** were obtained by conventional heating (at 170°C) after 4 hours in 40 to 80 % yield, and were obtained by microwave (at 900 W), after 15 to 35 minutes in 60 to 100 % yield. The results are summarized in Table 1. The novel compounds were characterized by elemental analysis and spectroscopic methods.



Scheme 2

Table 1

Reaction times and yields using microwave and conventional heating

Entries	Compound	R	R'	Conventional heating		Microwave heating	
				Time (h)	Yield (%)	Time (mn)	Yield (%)
1	**(3)**	H	H	9	38	30	84
2	**(4)**	H	Br	9	48	40	69
3	**(11)**	Me	H	9	67	35	95
4	**(12)**	Et	H	11	65	38	70
5	**(13)**	Me	Br	11	67	40	57
6	**(14)**	Et	Br	9	62	32	68
7	**(5)**	H	H	4	40	20	84
8	**(6)**	H	Br	4	55	30	72
9	**(15)**	Me	H	4	65	15	83
10	**(16)**	Et	H	4	58	18	72
11	**(17)**	Me	Br	4	52	30	60
12	**(18)**	Et	Br	4	80	35	**100**

EXPERIMENTAL

General

All reactions were monitored by analytical thin layer chromatography (TLC) (E. Merck Co., Darmstadt, Germany), and revealed by UV light (254 nm–264 nm). Melting points were determined in open capillary tubes in a Büchi Melting Point M-560 and are uncorrected. The IR data were recorded on Perkin Elmer spectrophotometer in KBr discs. Intensities of IR bands were referred to as strong (s), medium (m), and broad. Nuclear magnetic resonance (NMR) spectroscopy was registered on a Bruker avance apparatus (300, 450 and 500 MHz) instrument. Chemical shifts were reported in parts per million (ppm, δ) downfield from tetramethylsilane. Proton coupling patterns were described as singlet (s), doublet (d), triplet (t), triplet doublet (td), quartet (q), multiplet (m). MS experiments were performed on a Bruker Daltonics microTOF spectrometer. Elemental analyses were carried on a "Flash 2000" apparatus. MW irradiation was conducted in a domestic MW oven (Samsung GE614ST).

General procedure for the synthesis of 2-methyl quinolin-4-carboxylic acid derivatives (1)-(2)

A mixture of isatin derivative (0.035 mol), KOH (0.28 mol) and H_2O (32 mL) was stirred for 5 minutes at room temperature. Acetone (0.836 mol) was added while stirring, and the mixture was refluxed for 8 hours. After cooling, the pH of the mixture was brought to a pH between 5 and 6 by the addition of hydrochloride acid (10%), the obtained precipitate was filtered and washed with water then dried.

2-methylquinoline-4-carboxylic acid* (1):* This compound was obtained as a brown powder; (64 %); mp: 240 °C. lit. 238–240°C; IR (KBr, cm^{-1}): 3500 (broad, OH), 1690 (s, C=O); ^{1}H NMR (DMSO): δ 2.52 (s, 3H, C<u>H</u>$_3$), 7.65 (td, 1H, H6), 7.75 (td, 1H, H7), 7.82 (s, 1H, H3), 8.02 (d, 1H, H8), 8.62 (1H, d, H5), 13.80 (sL, 1H, COO<u>H</u>); ^{13}C NMR: δ 24.70 (<u>C</u>H$_3$), 122.70,

122.77, 125.35, 126.91, 128.86, 129.65, 136.36, 148.13, 158.70, 167.65.

6-bromo-2-methylquinoline-4-carboxylic acid* (2):* This compound was obtained as a brown powder; (85%); mp: 261°C. lit. 259-260°C; IR (KBr, cm^{-1}): 3400 (broad, OH), 1650 (s, C=O), 1150, 557.

General procedure for the synthesis of alkyl 2-methylquinolin-4-carboxylate (7)-(10)

In a 100 mL flask; 2-methylquinoline-4-carboxylic acid (3 mmol), alcohol (25 mL) and sulfuric acid (1 mL) were introduced. The mixture was heated under reflux. The reaction was controlled by thin layer chromatography (TLC). At the end of the reaction, the mixture was concentrated under reduced pressure and the residue was neutralized with saturated sodium carbonate solution. The organic phase was extracted with chloroform (or ethyl acetate), dried over anhydrous magnesium sulfate, filtered and evaporated.

Methyl 2-methylquinoline-4-carboxylate* (7):* This compound was obtained as a beige powder; (67%) ; mp: 95°C; IR (KBr, cm^{-1}): 1723 (s, C=O), 1593 (m, C=N), 1243; ^{1}H NMR ($CDCl_3$): δ 2.5 (s, 3H, C<u>H</u>$_3$), 3.8 (s, 3H, -OC<u>H</u>$_3$), 7.51 (td, 1H, H6), 7.64 (td, 1H, H7), 7.73 (s, 1H, H3), 8.00 (dd, 1H, H8), 8.61 (dd, 1H, H5); ^{13}C NMR ($CDCl_3$): δ 25.23 (<u>C</u>H$_3$), 52.62 (O<u>C</u>H$_3$), 123.21, 125.37, 127.18, 129.21, 129.71, 135.06, 149.38, 158.42, 166.67 (<u>C</u>O).

Ethyl 2-methylquinoline-4-carboxylate* (8):* This compound was obtained as a brown powder; (55%); mp: 70°C ; IR (KBr, cm^{-1}): 1700 (s, C=O), 1590 (m, C=N), 1300, 1110; ^{1}H NMR ($CDCl_3$): δ 1.37 (t, 3H, C<u>H</u>$_3$), 2.50 (s, 3H, 2-C<u>H</u>$_3$), 4.41 (q, 2H, -O-C<u>H</u>$_2$), 7.48 (td, 1H, H6), 7.62 (td, 1H, H7), 7.68 (s, 1H, H3), 7.97 (dd, 1H, H8), 8.58 (dd, 1H, H5); ^{13}C NMR ($CDCl_3$): δ 13.28 (CH_2- <u>C</u>H$_3$), 24.22 (<u>C</u>H$_3$), 60.73 (O-<u>C</u>H$_2$-), 122.06, 122.33, 124.53, 126.06, 128.18, 134.41, 147.79, 157.41, 165.33 (<u>C</u>O)

Methyl 6-bromo-2-methylquinoline-4-carboxylate* (9):* This compound was obtained as a brown powder; (87%); mp : 159.9°C; IR (KBr, cm^{-1}): 1717 (s, C=O), 1598 (m, C=N), 1201, 655 (m, C-Br); ^{1}H NMR ($CDCl_3$): δ 2.80 (s, 3H, C<u>H</u>$_3$), 4.04 (s, 3H, -O-C<u>H</u>$_3$), 7.80 (d, 1H, H7), 7.84 (s, 1H, H3), 7.94 (d, 1H, H8), 8.93 (s, 1H, H5); ^{13}C NMR ($CDCl_3$): δ 25.22 (<u>C</u>H$_3$), 52.85 (<u>C</u>H$_3$-O), 121.72, 124.19, 124.46, 127.84, 130.75, 133.29, 133.84, 147.40, 158.99, 166.2 (<u>C</u>O)

Ethyl 6-bromo-2-methylquinoline-4-carboxylate* (10):* This compound was obtained as a light brown powder; (68 %); mp: 110°C ; IR (KBr, cm^{-1}): 1721 (s, C=O), 1587 (m, C=N), 1241, 654 (C-Br); ^{1}H NMR ($CDCl_3$): δ 1.47 (t, 3H, CH_2-C<u>H</u>$_3$), 2.76 (s, 3H, 2-C<u>H</u>$_3$), 4.49 (q, 2H, -C<u>H</u>$_2$-CH_3), 7.78 (d, 1H, H7), 7.81 (s, 1H, H3), 7.91 (d, 1H, H8), 8.93 (s, 1H, H5), ^{13}C NMR ($CDCl_3$): δ: 14.43 (CH_2- <u>C</u>H$_3$), 25.41 (<u>C</u>H$_3$), 62.16 (O-<u>C</u>H$_2$-), 121.73, 124.15, 124.64, 128.01, 130.93, 133.33, 134.32, 147.58, 159.13 (C2), 165.91 (C=O).

General Method for the synthesis of quinoline N-Oxide derivatives: (3)-(4); (11)-(14)

Conventional heating

30% hydrogen peroxide (0.13 mL) was added to a solution of the 2-methylquinoline-4-carboxylic acid (1.4 mmol) in glacial acetic acid (0.42 mL). The reaction mixture was warmed to 65-70 °C for 3 hours, then hydrogen peroxide (1 mL) was added and the mixture was stirred at 65-70 °C for an additional 6 hours. The mixture was concentrated, basified with saturated sodium carbonate solution, and extracted with chloroform. The organic layer was dried and the solvent was removed on a rotary evaporator.

Microwave-assisted Synthesis

In a small beaker, 30% hydrogen peroxide solution (0.13 mL) was added to a solution of 2-methylquinoline derivatives (7)-(10) (1.4 mmol) in glacial acetic acid (0.42 mL), the beaker was covered with a watch glass, and then the solution was subjected to a 100 W microwave irradiation for a convenient time (The reaction was monitored by TLC). The solution was concentrated, basified with saturated sodium carbonate solution and extracted with chloroform. The organic layer was dried and the solvent was removed on a rotary evaporator.

For the acid derivatives (1)-(2) at the end of reaction, cold water (2 mL) was poured into the beaker, the precipitate which formed was left in a refrigerator overnight, then filtered, washed with water and dried.

2-methylquinoline-4-carboxylic acid N-oxide* (3):* This compound was obtained as a yellow powder; mp 233.1°C. IR (KBr, cm^{-1}): 3450 (broad, O-H), 1670 (s, C=O), 1320 (m, N-O), 1150 (m, C-O); ^{1}H NMR (DMSO): δ 2.63 (s, 3H, CH_3); 7.83-9.05 (m, 5H, H aromatiques), 13.70 (s_L, COOH); ^{13}C NMR (DMSO): δ 18.47 (CH_3), 119.42, 122.75, 126.97, 127.09, 129.38, 130.63, 130.70, 141.84, 144.78, 166.81.

6-bromo-2-methylquinoline-4-carboxylic acid N-oxide* (4):* This compound was obtained as a yellow powder; mp : 217.6°C; IR (KBr, cm^{-1}): 3109 (s, O-H), 1716 (m, C=O), 1557 (m, C=N), 1323 (m, N-O), 705 (m, C-Br); ^{1}H NMR ($CDCl_3$): δ 2.55 (s, 3H, C<u>H</u>$_3$), 7.91 (d, 1H, H7), 8.19 (s, 1H, H3), 8.47 (d, 1H, H8), 9.19 (s, 1H, H5); ^{13}C NMR ($CDCl_3$): δ 17.88 (<u>C</u>H$_3$), 120.39, 121.35, 122.79, 127.79, 128.52, 132.87, 140.24, 144.93, 165.90 (C=O).

Methyl 2-methylquinoline-4-carboxylate N-oxide* (11):* This compound was obtained as an orange powder; mp: 133.9 °C; IR (KBr, cm^{-1}): 1702 (s, C=O), 1591 (m, C=N), 1325 (m, N-O); ^{1}H NMR (D_2O): δ 2.58 (s, 3H, C<u>H</u>$_3$), 3.96 (s, 3H, OC<u>H</u>$_3$), 7.51-8.99 (m, 5H, Ar-H); ^{13}C NMR ($CDCl_3$): δ 18.59 88 (<u>C</u>H$_3$), 52.58 (O-<u>C</u>H$_3$), 119.57, 122.22, 126.15, 126.62, 126.98, 129.05, 130.32, 142.24, 144.60, 165.36 (C=O).

Ethyl 2-methylquinoline-4-carboxylate N-oxide* (12):* This compound was obtained as a yellow powder; mp: 97°C; IR (KBr, cm^{-1}): 1710 (s, C=O), 1509 (m, C=N), 1221 (m, N-O); ^{1}H NMR ($CDCl_3$): δ 1.45 (t, 3H, C<u>H</u>$_3$-CH_2), 2.70 (s, 3H, C<u>H</u>$_3$), 4.46 (q, 2H, CH_3-C<u>H</u>$_2$-), 7.66 (td, 1H, H6), 7.75 (td, 1H, H7), 8.0 (s, 1H, H3), 8.77 (dd, 1H, H8), 8.98 (dd, 1H, H5); ^{13}C NMR ($CDCl_3$): δ 14.45 (<u>C</u>H$_3$-CH_2-), 18.74 (<u>C</u>H$_3$), 61.83 (<u>C</u>H$_2$-CH_3), 119.67, 122.64, 126.15, 126.75, 127.12, 129.10, 130.38, 142.32, 144.68 (C9), 165.07 (<u>C</u>=O), *Anal.* Calcd for $C_{13}H_{13}NO_3$: N, 6.06; C, 67.52; H, 5.67; found: N, 6.32; C, 67.56; H, 5.68.

Methyl 6-bromo-2-methylquinoline-4-carboxylate N-oxide* (13):* This compound was obtained as a yellow powder; mp : 160.7°C; IR (KBr, cm^{-1}): 1717 (s, C=O), 1553 (m, C=N), 1322 (m, N-O), 1228 (m, C-O), 653 (m, C-Br); ^{1}H NMR ($CDCl_3$): δ 2.69 (s, 3H, C<u>H</u>$_3$), 4.01 (s, 3H, O-CH_3), 7.82 (dd, 1H, H7), 8.06 (s, 1H, H3), 8.63 (d, 1H, H8), 9.23 (d, 1H, H5); ^{13}C NMR ($CDCl_3$): δ 18.77 (<u>C</u>H$_3$), 52.91 (O<u>C</u>H$_3$), 121.21, 121.58, 124.44, 127.37, 128.19, 129.13, 133.91, 141.17, 145.28, 165.00 (C=O).

Ethyl 6-bromo-2-methylquinoline-4-carboxylate N-oxide* (14):* This compound was obtained as a yellow powder ; mp : 115.1°C; IR (KBr, cm^{-1}): 1716 (s, C=O), 1558 (m, C=N), 1322 (m, N-O), 654 (m, C-Br); ^{1}H NMR (DMSO) δ 1.39 (t, 3H, CH_3), 2.57 (s, 3H, 2-C<u>H</u>$_3$), 4.42 (q, 2H, -O-C<u>H</u>$_2$-CH_3), 7.99 (dd, 1H, H7), 8.23 (s, 1H, H3), 8.53 (d, 1H, H8), 9.12 (d, 1H, H5); ^{13}C NMR (DMSO) δ 14.09 (-CH_2-<u>C</u>H_3), 17.93 (<u>C</u>H_3), 61.63 (<u>C</u>H_2-O-), 119.62, 121.50, 127.50, 127.58, 128.31, 133.16, 140.27, 145.17, 164.16 (C=O); *Anal.* Calcd for $C_{13}H_{12}BrNO_3$: N, 4.52; C, 50.34; H, 3.90; found: N, 4.57; C, 48.91; H, 3.81.

General method for the synthesis of 2-(acethoxymethyl) quinoline derivatives :(5)-(6), (15)-(18)

Conventional heating

A mixture of the N-Oxide quinoline derivative (0.4 mmol) and acetic anhydride (2 mL) was heated under reflux. After 4 hours, the solution was concentrated to give the desired product.

Microwave-assisted Synthesis

A mixture of the N-Oxide quinoline derivative (0.4 mmol) and acetic anhydride (2 mL) was properly mixed in a beaker. The obtained mixture was subjected to microwave irradiation (900 W); (the reaction was monitored by TLC). When the reaction was completed, the solution was concentrated on a rotary evaporator to afford the desired product.

2-(acethoxymethyl)quinoline-4-carboxylic* (5):* This compound was obtained as an orange powder; mp: 216.5°C; IR (KBr, cm^{-1}): 3066 (broad, OH), 1742 (s, C=O), 1701 (s, C=O), 1598 (m, C=N), 1233, 774; ^{1}H NMR (DMSO): δ 2.11 (s, 3H, C<u>H</u>$_3$), 5.30 (s, 2H, -C<u>H</u>$_2$), 7.71 (td, 1H, H6), 7.78 (td, 1H, H7), 7.80 (s, 1H, H3), 8.11 (d, 1H, H8), 8.48 (dd, 1H, H5); ^{13}C NMR (DMSO) δ 20.37 (-<u>C</u>H_3), 66.08 (-<u>C</u>H_2-O), 120.28, 123.28, 125.58, 128.27, 128.97, 30.46, 147.63, 156.32, 160.35, 168.41, 171.12; hrms. calculated for $C_{13}H_{11}NO_4H$: 246.0761 found 246.0777*; Anal.* Calcd. for $C_{13}H_{11}NO_4$: N ,5.71; C, 63.67, H, 4.52 found: N , 5.77; C, 62.38, H,4.40.

2-(acetoxymethyl)-6-bromoquinoline-4-carboxylic* (6):* This compound was obtained as an orange powder; mp : 195.7°C; IR (KBr, cm^{-1}): 3109; 1748 (s, C=O ester), 1740 (s, C=O acid), 1597 (m, C=N), 1237 (m, C-O), 706 (m, C-Br); ^{1}H NMR (DMSO): δ 2.17 (s, 3H, C<u>H</u>$_3$), 5.35 (s, 2H, -C<u>H</u>$_2$O-), 7.97-8.02 (m, 3H, H7, H8, H3), 8.95 (d, 1H, H5); ^{13}C NMR (DMSO) δ 20.62 (-<u>C</u>H_3), 66.20 (-<u>C</u>H_2-O), 121.49, 121.57, 124.98, 127.61, 131.43, 133.16, 135.43, 146.43, 157.07, 166.76, 170.16 (C=O); *Anal.* Calcd for $C_{13}H_{10}BrNO_4$: N, 4.32; C, 48.17; H, 3.11 found: N, 4.62; C, 47.11; H, 3.11.

Methyl 2-(acethoxymethyl) quinoline-4-carboxylate* (15):* This compound was obtained as an orange powder; mp 100.5°C; IR (KBr, cm^{-1}): 1729 (s, C=O), 1728 (s, C=O), 1586 (m, C=N), 1228; ^{1}H NMR (DMSO): δ 2.14 (s, 3H, C<u>H</u>$_3$), 3.9 (s, 3H, COOC<u>H</u>$_3$), 5.35 (s, 2H, C<u>H</u>$_2$-O), 7.58 (td, 1H, H6), 7.70 (td, 1H, H7), 7.89 (s, 3H, H3), 8.05 (d, 1H, H8), 8.6 (dd, 1H, H5); ^{13}C NMR (DMSO) δ 20.92, 52,73, 67.12, 120.79, 124.39, 125.50, 128.29, 129.80, 130.06, 135.83, 148.62, 155.71, 166.63, 170.79; hrms: calculated for $C_{14}H_{13}NO_4H$: 260.0917 found 260.0887; *Anal.* Calcd for $C_{14}H_{13}NO_4$: N, 5.40; C, 64.86; H, 5.05 found: N, 5.48; C, 64.78; H, 5.03.

Ethyl 2-(acetoxymethyl)quinoline-4-carboxylate* (16):* This compound was obtained as a brown oil; ^{1}H NMR (DMSO): δ 1.4 (t, 3H, -CH_2- C<u>H</u>$_3$), 2.1 (s, 3H, C<u>H</u>$_3$), 4.4 (q, 2H, -C<u>H</u>$_2$-CH_3), 5.3 (s, 2H, -C<u>H</u>$_2$-O), 7.74 (td, 1H, H6), 7.85 (td, 1H, H7), 7.93 (s, 1H, H3), 8.08 (dd, 1H, H8), 8.57 (dd, 1H, H5); ^{13}C NMR (DMSO) δ 14.49 (-CH_2- <u>C</u>H_3), 21.18 (<u>C</u>H_3), 62.38 (-<u>C</u>H_2-CH_3), 66.83(-<u>C</u>H_2-O), 120.69, 123.84, 125.59, 128.68, 129.86, 130.77, 136.51, 148.19, 156.71, 166.07, 170.65; *Anal*. Calcd for $C_{15}H_{15}NO_4$: N, 5.13; C, 65.92; H, 5.53; found: N, 5.53; C, 67.22; H, 5.34.

Methyl 2-(acetoxymethyl)-6-bromo quinoline-4-carboxylate* (17):* This compound was obtained as an orange powder; mp : 101.2°C; IR (KBr, cm^{-1}): 1725 (s, C=O), 1596 (m, C=N), 1224, 1201, 651 (m, C-Br); ^{1}H NMR ($CDCl_3$): δ 2.2 (s, 3H, -C<u>H</u>$_3$), 4.01 (s, 3H, -O-C<u>H</u>$_3$), 5.38 (s, 2H, -C<u>H</u>$_2$-O), 7.82 (dd, 1H, H7), 7.96 (s, 1H, H3), 7.99 (d, 1H, H8), 8.97 (d, 1H, H5); ^{13}C NMR ($CDCl_3$): δ 21.05 (CH_3), 53.11 (O-CH_3), 67.03 (-CH_2-), 121.82, 123.10, 125.57, 128.08, 131.43, 133.81, 134.70, 147.34, 156.36, 166.05, 170.73; *Anal*. Calcd for $C_{12}H_{10}BrNO_3$: N, 4.73; C, 48.67; H, 3.40 found: N, 4.79; C, 48.24; H, 3.37.

***Ethyl-2-(acetoxymethyl)-6-bromo quinoléine-4-carboxylate* (18):** This compound was obtained as a brown oil; IR (KBr, cm^{-1}): 1729 (s, C=O), 1728 (s, C=O), 656 (m, C-Br); ^{1}H NMR (DMSO): δ 1.4 (t, 3H, -CH_2-C<u>H</u>$_3$), 2.16 (s, 3H, -C<u>H</u>$_3$), 4.47 (q, 2H, -O-C<u>H</u>$_2$), 5.37 (s, 2H, -C<u>H</u>$_2$-O), 7.99-8.04 (m, 3H, H7, H3, H8), 8.58 (d, 1H, H5); ^{13}C NMR (DMSO): δ 22.39, 23.22, 66.20, 67.39, 121.48, 124.75, 127.42, 128.66, 131.55, 131.60, 133.44, 146.41, 157.18, 165.09, 170.20; *Anal*. Calcd for $C_{15}H_{14}BrNO_4$: N, 3.98; C, 51.16; H, 4.01 found: N, 3.72; C, 48.16; H, 4.10.

CONCLUSION

In this report, we have used conventional and microwave heating to synthesize quinoline N-Oxide and 2-acetoxyquinoline derivatives. In all cases, best yields and short reaction times were obtained by microwave synthesis, which proves the effectiveness of the microwave assisted synthesis as an ecological alternative to the conventional heating.

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