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Microwave Assisted Gould-Jacobs Reaction for Synthesis of 3-Acetyl-4-hydroxyquinoline Derivatives

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Different types of quinoline derivatives have been synthesized by microwave irradiation and reaction yields were compared with reported classical methodology. The emphasis on this research project was to reduce reaction times and enhance the yields of the title compounds especially by using readily available materials including aryl amines. The key intermediate formed by condensation of microwave assisted multicomponent reaction under solvent free conditions was further cyclized through a heat mediated Gould-Jacobs cyclization reaction to get substituted quinolines. A study was also made to establish one pot synthesis of quinoline derivatives in order to eliminate the purification/drying step to get key intermediate but the product yields were found to be very poor than those in the classical methodology. The synthesized compounds were characterized and identified, using different spectroscopic tools *i.e.*, FT-IR, mass spectrometry, elemental analysis and ^{1}H NMR.

Keywords: Microwave irradiation, Substituted quinolines, Gould-Jacobs reaction.

INTRODUCTION

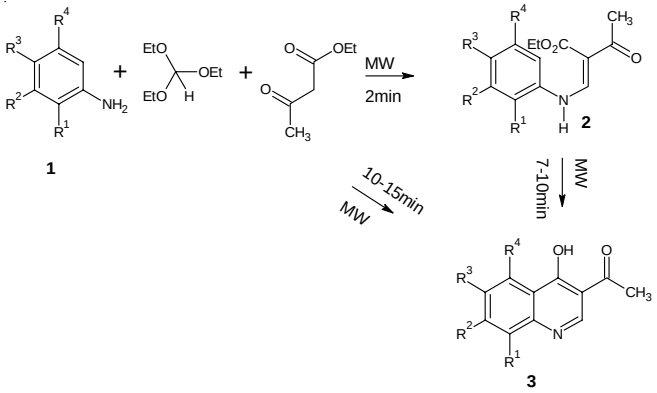
An important class of broad-spectrum antibiotics is based on quinoline molecules[1-3] that were traditionally obtained by refluxing an aniline and diethyl ethoxymethylenemalonate for several hours often in low yield[4]. In classical work, reactions were carried out at reflux temperature for several hours and cyclization was performed in different high boiling liquids such as diphenyl ether, paraffin oil, high boiling mineral oils *etc.* resulting in low yields and other side reactions such as decomposition. Heating the reaction mixture by microwaves to temperatures above the boiling points, with or without solvents, improves the yields and shortens the reaction time dramatically[5]. Gould-Jacobs reaction was reported in 1939 to prepare 4-quinolone derivatives[6]. Although, a number of reactions have been reported with different modification in the Gould-Jacobs reaction but in every reported work ethoxymethylenemalonate was used as a starting material[5,7]. The preparation of these ethoxymethylenemalonates is a tedious job and its stability for long time is another problem as well as a risk factor[8-13] for maintaining the smooth production of such a pharmacologically important intermediate.

EXPERIMENTAL

Analytical reagent grade chemicals and solvents including aryl amines, ethyl acetoacetate, triethyl orthoformate, N,N-dimethylformamide, toluene, acetic acid, ethanol, methanol, ethyl acetate, *n*-hexane and petroleum ether (40-60) ºC were purchased from Across Organics, Sigma- Aldrich and Lab Scan and were used without any further purification. Melting points were taken by electro thermal open capillary method and are uncorrected. Microwave synthesis was preformed using a conventional (unmodified) domestic MW oven. NMR spectra were measured on a (Jeol JNM-ECA300) 300 MHz spectrometer. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane (TMS). Electron ionization technique was used on Perkin Elmer Clarus 680 GC-MS instrument at 70 eV for the mass spectra. Perkin Elmer FTIR was used for IR spectra[15,16].

General procedure for the preparation of β-anilinoacrylic ester (2a-f) (intermediate) through microwave irradiation: Equimolar (10 mmol) quantities of ethyl acetoacetate, triethyl orthoformate and aryl amine **1** were mixed and microwave irradiated without solvent for two minutes at 120 ºC and cooled. Crystals formed upon cooling, strained, washed

with pet. ether (40-60 °C), dried and recrystallized from ethanol to get key intermediates (**2a-f**) as shown in **Scheme-I**, Table-1.



Scheme-I

Ethyl-2-{[(3-chlorophenyl)amino]methylidene}-3-oxobutanoate (2a): White crystals, m.p. 87 ºC, IR (KBr, ν_{max}, cm^{-1}): 2923.0 (NH, Str), 1706.4 (C=O, Str, Ester), 1637.3 (C=O, Str, Ac), 1597.5 (NH, bend), 795.1 and 762.9 (C-Cl, Str). Anal. calcd. (%) for $C_{13}H_{14}NO_3Cl$ (267.7): C, 58.33; H, 5.27; Cl, 13.24; N, 5.23. Found (%): C, 57.98; H, 5.24; Cl, 13.16; N, 5.21.

Ethyl-2-{[(2-methoxyphenyl)amino]methylidene}-3-oxobutanoate (2b): White crystals, m.p. 108 ºC, IR (KBr, ν_{max}, cm^{-1}): 2923.0 (NH, Str), 1696.8 (C=O, Str, Ester), 1629.6 (C=O, Str, Ac), 1596.3 (NH, Bend). Anal. calcd. (%) for $C_{14}H_{17}NO_4$ (263.29): C, 63.86; H, 6.51; N, 5.32. Found (%): C, 63.48; H, 6.47; N, 5.29.

Ethyl-2-{[(2-methylphenyl)amino]methylidene}-3-oxobutanoate (2c): White crystals, m.p. 154 ºC, IR (KBr, ν_{max}, cm^{-1}): 3018.19 (NH, Str), 1720.0 (C=O, Str, Ester), 1660.45 (C=O, Str, Ac), 1580.1 (NH, Bend). Anal. calcd. (%) for $C_{14}H_{17}NO_3$ (247.29): C, 68.00; H, 6.93; N, 5.66. Found (%): C, 67.69; H, 6.92; N, 5.64.

Ethyl-2-{[(4-bromophenyl)amino]methylidene}-3-oxobutanoate (2d): White crystals, m.p. 162 ºCC, IR (KBr, ν_{max}, cm^{-1}): 3301.9 (NH, Str), 1725.4 (C=O, Str, Ester), 1629.3 (C=O, Str, Ac), 1593.1 (NH, Bend), 568.53 (C-Br, Str). Anal. calcd. (%) for $C_{13}H_{14}NO_3Br$ (312.16): C, 50.02; H, 4.52; Br, 25.60; N, 4.49. Found (%): C, 49.95%; H, 4.51; Br, 25.54; N, 4.47.

Ethyl-2-{[(3-methoxyphenyl)amino]methylidene}-3-oxobutanoate (2e): White crystals, m.p. 92 ºC, IR (KBr, ν_{max}, cm^{-1}): 3031.9 (NH, Str), 1699.56 (C=O, Str, Ester), 1635.68 (C=O, Str, Ac), 1608.28 (NH, Bend). Anal. calcd. (%) for $C_{14}H_{17}NO_4$ (263.29): C, 63.86; H, 6.51; N, 5.32. Found (%): C, 63.58; H, 6.49; N, 5.30.

Ethyl-2-{[(4-nitrophenyl)amino]methylidene}-3-oxobutanoate (2f): Yellow crystals, m.p. 210 ºC, IR (KBr, ν_{max}, cm^{-1}): 2925.2 (NH, Str), 1710.9 (C=O, Str, Ester), 1688.8 (C=O, Str, Ac), 1587.9 (NH, Bend), 1477.5 & 1358.0 (Arom. NO_2, Str). Anal. calcd. (%) for $C_{13}H_{14}N_2O_5$ (278.26): C, 56.11; H, 5.07%; N, 10.07. Found (%): C, 56.01; H, 5.02; N, 10.03.

General procedure of cyclization to synthesize quinolines through microwave assisted Gould-Jacobs reaction: Dried intermediates (**2a-f**) obtained were cyclized with four times amounts by volume diphenyl ether as solvent by microwave irradiation at 250 ºC for 10-15 min, cooled to room temperature and diluted with *n*-hexane, filtered, dried and recrystallized from N,N-dimethyl formamide (DMF) to afford (**3a-f**) as shown in **Scheme-I**, Table-1.

3-Acetyl-4-hydroxy-7-chloroquinoline (3a): Solid, m.p. 230 ºC, IR (KBr, ν_{max}, cm^{-1}): 3073.8 (OH, Str, H-bonded), 1665.85, 1609.39 (C=O, Str), 1352.85, 1303.87 and 1200.14 (OH, Bend) EIMS: *m/z*: $221M^+$; $223M^+$+2, 206, 178, 150, 138, 123. ^{1}H NMR (300MHz, DMSO-d_6): δ ppm 8.54 (s, 1H, ArH), 8.16 (d, *J* = 8.62Hz, 1H, ArH), 7.61 (s, 1H, ArH), 7.33 (d, *J* = 8.64 Hz, 1H, ArH), 2.56 (s, 3H, $AcCH_3$). Anal. calcd. (%) for $C_{11}H_8NO_2Cl$ (221.64): C, 59.61; H, 3.64; Cl, 16.00; N, 6.32. Found (%): C, 56.25; H, 3.62; Cl, 15.93; N, 6.29.

3-Acetyl-4-hydroxy-5-chloroquinoline (3aa): Solid, m.p. 243 ºC, IR (KBr, ν_{max}, cm^{-1}): 3073.0 (OH, Str, H-bonded), 1671.48, 1608.24 (C=O, Str), 1350.12, 1303.33 and 1197.71 (OH, Bend). ^{1}H NMR (300 MHz, DMSO-d_6): δ ppm 8.41 (s, 1H, ArH), 8.16 (d, 1H, ArH), 7.53 (t, 1H, ArH), 7.31 (d, 1H, ArH), 2.56 (s, 3H, $AcCH_3$).

3-Acetyl-4-hydroxy-8-methoxyquinoline (3b): Solid, m.p. 244 ºC, IR (KBr, ν_{max}, cm^{-1}): 3054.68 (OH, Str, H-bonded), 1659.75, 1615.30 (C=O, Str), 1361.14, 1274.21 and 1195.4 (OH, Bend) EIMS: *m/z*: $217M^+$, 202, 174, 143, 115, 100. ^{1}H NMR (300MHz, $CDCl_3$): δ ppm 9.225 (s, 1H, ArOH), 8.540 (s, 1H, ArH), 7.984 (d, *J* = 8.4 Hz, 1H, ArH), 7.337 (t, *J* = 8.1 Hz, 1H, ArH), 7.0875 (d, *J* = 7.5 Hz, 1H, ArH), 3.999 (s, 3H, $ArOCH_3$), 2.786 (s, 3H, $AcCH_3$). Anal. calcd. (%) for $C_{12}H_{11}NO_3$ (217.22): C, 66.35; H, 5.10; N, 6.45. Found (%): C, 66.96; H, 5.07; N, 6.41.

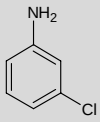
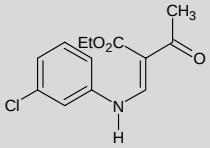
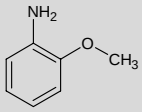
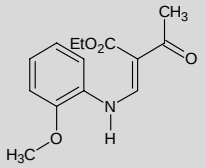
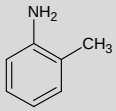
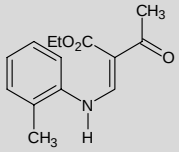
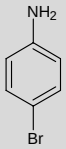
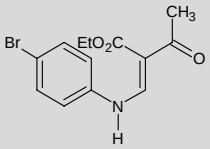
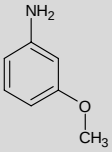
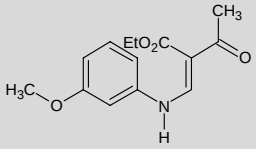
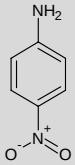
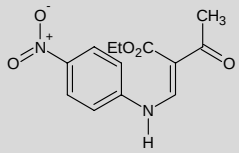
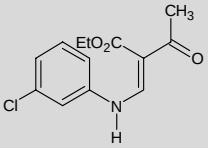
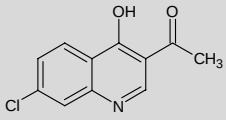
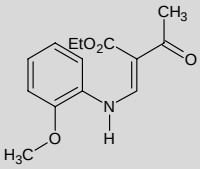
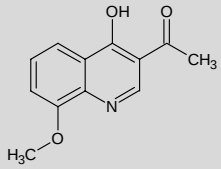
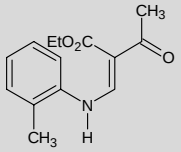
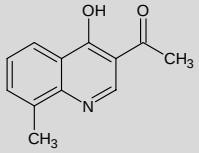
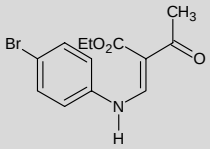
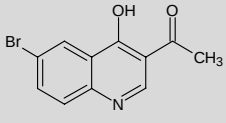
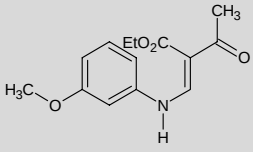
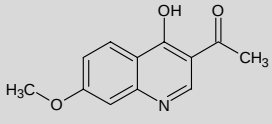
3-Acetyl-4-hydroxy-8-methylquinoline (3c): Solid, m.p. 266 ºC, IR (KBr, ν_{max}, cm^{-1}): 3198.5 (OH, Str, H-bonded), 1671.50, 1615.1 (C=O, Str), 1342.40, 1280.50 and 1190.50 (OH, Bend) EIMS: *m/z*: $201M^+$, 186, 158, 143, 115, 103, 91. ^{1}H NMR (300 MHz, DMSO-d_6): δ ppm 8.47 (s, 1H, ArH), 8.07 (d, *J* = 7.2Hz, 1H, ArH), 7.47 (d, *J* = 8.1 Hz, 1H, ArH), 7.23 (t, *J* = 7.5, 1H, ArH), 2.59 (s, 3H, $ArCH_3$), 2.50 (s, 3H, $AcCH_3$). Anal. calcd. (%) for $C_{12}H_{11}NO_2$ (201.22): C, 71.63; H, 5.51; N, 6.96. Found (%): C, 71.21; H, 5.48; N, 6.92.

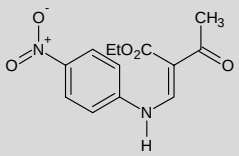
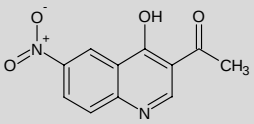
3-Acetyl-4-hydroxy-6-bromoquinoline (3d): Solid, m.p. 286 ºC, IR (KBr, ν_{max}, cm^{-1}): 3090.7 (OH, Str, H-bonded), 1644.58, 1611.52 (C=O, Str), 1341.46, 1300.41 and 1206.39 (OH, Bend) EIMS: *m/z*: $265M^+$, $267M^{+2}$, 251, 223, 144, 116, 101. ^{1}H NMR (DMSO-d_6): δ ppm 8.56 (s, 1H, ArH), 8.29 (s, 1H, ArH), 7.81 (d, *J* = 8.7 Hz, 1H, ArH), 7.57 (d, *J* = 8.8 Hz, 1H, ArH), 2.50 (s, 3H, $AcCH_3$). Anal. calcd. (%) for $C_{11}H_8NO_2Br$ (266.09): C, 49.65; H, 3.03; Br, 30.03; N, 5.26. Found (%): C, 49.34; H, 3.00; Br, 29.85; N, 5.23.

3-Acetyl-4-hydroxy-7-methoxyquinoline (3e): Solid, m.p. 258 ºC, IR (KBr, ν_{max}, cm^{-1}): 3118.12 (OH, Str, H-bonded), 1662.74, 1625.83 (C=O, Str), 1355.28, 1303.66 and 1199.10 (OH, Bend) EIMS: *m/z*: $217M^+$, 202, 174, 159, 143, 115, 100. ^{1}H NMR (DMSO-d_6): δ ppm 8.45 (s, 1H, ArH), 8.12 (d, *J* = 8.6 Hz, 1H, ArH), 7.04 (d, *J* = 7.8 Hz, 1H, ArH), 7.02 (s, 1H, ArH), 3.87 (s, 3H, $ArOCH_3$), 2.51 (s, 3H, AcH). Anal. calcd. (%) for $C_{12}H_{11}NO_3$ (217.22): C, 66.35; H, 5.10; N, 6.45. Found (%): C, 65.96; H, 5.08; N, 6.43.

3-Acetyl-4-hydroxy-6-nitroquinoline (3f): Solid, m.p. 296 ºC, IR (KBr, ν_{max}, cm^{-1}): 3088.0 (OH, Str, H-bonded), 1665.80, 1575.2 (C=O, Str), 1502.6 (Ar- NO_2,), 1338.10 (Ar-

TABLE-1
COMPARATIVE STUDY OF MICROWAVE ASSISTED GOULD-JACOBS REACTION WITH OLD CLASSICAL METHODOLOGY FOR THE SYNTHESIS OF 3-ACETYL-4-HYDROXY QUINOLINE DERIVATIVES

Entry	Aryl amine	Reaction time (min)	Yield (%)	Reaction time (h)	Yield (%)	Product
2a		2	91	16	67	
2b		2	94	16	64	
2c		2	91	16	60	
2d		2	90	16	52	
2e		2	96	16	61	
2f		2	92	16	45	
3a		10	59	0.5	39	
3b		12	68	0.5	51	
3c		10	72	0.5	49	
3d		15	65	0.5	38	
3e		10	74	0.5	49	

3f		15	59	0.5	33	

NO_2), 1287.20 and 1201.65 (OH, Bend) EIMS: *m/z*: 232M^+, 217, 189, 143, 115, 100. ^{1}H NMR (DMSO-d_6): δ ppm 8.68 (s, 1H, ArH), 8.71 (s, 1H, ArH), 8.37 (d, *J* = 8.1 Hz, 1H, ArH), 7.91 (d, *J* = 7.8 Hz, 1H, ArH), 2.50 (s, 3H, $AcCH_3$). Anal. calcd. (%) for $C_{11}H_8N_2O_4$ (232.19): C, 56.90; H, 3.47; N, 12.06. Found (%): C, 56.56; H, 3.45; N, 12.01.

RESULTS AND DISCUSSION

In this work, we describe a highly efficient multi-component microwave assisted Gould-Jacobs reaction for the synthesis of 3-acetyl-4-hydroxyquinoline derivatives using readily available staring materials in good yield. The yield of key intermediate (**2**) was always excellent *i.e.* more than 90 %. The first step to get key intermediate **(2)**, was achieved by Michael addition/elimination mechanism and have been reported by using traditional wet classical synthesis with ethoxymethylenemalonate by refluxing in ethanol for over night or by using a base such as potassium hydroxide[14]. By replacing the old methodology with microwave we have developed a new avenue in such addition/elimination reactions with much shorter reaction time and another step towards green chemistry. This step is solvent free and also an example of one pot multi component reaction eliminating the use of ethoxymethylenemalonate.

The second step to cyclize the key intermediate **(2)** especially by Gould-Jacobs reaction, is an electrophilic aromatic substitution reaction to afford the quinoline derivatives as shown in Table-1. This step was performed by using diphenyl ether as a solvent with four times dilution by weight to the reactants to be cyclized. Purification procedures were simple because cyclized products were precipitated out by the addition of *n*-hexane and further recrystallized to get the pure quinoline derivatives. However it is interesting to note that only *meta*-substituted aryl amine produced two isomers instead of one product. The product **3a**, which should be 7-chloro derivative, gave a mixture of 7-chloro and 5-chloro products with 8.7 % of 5-chloro derivatives only. However in case of **3e**, which should be a mixture of **5** and 7-methoxy, products was always a pure 7-methoxy derivative. This could be attributed to the steric hindrance of the bulky methoxy group causes hindrance in aromatic substitution reaction. This abnormality was confirmed by NMR spectroscopic tool. The effect of solvent to the cyclization position was also investigated and found that by changing solvent from diphenyl ether to paraffin liquid the ratio of the **5** and 7-chloro isomers was inverted.

In this project we have eliminated the use of ethoxymethylenemalonate due to the stability problems for longer duration and also to keep in view the risk of peroxide generation[13]. This work could be advantageously manipulated by using suitable acetoacetate esters and aryl amines (**1**) to get the desired quinoline derivatives. An attempt to carry one pot reaction for **3** resulted in low yields accompanied by extensive decomposition and charring.

Conclusion

The study showed enhanced and efficient synthesis of important broad spectrum antibiotic intermediate 3-acetyl-4-hydroxyquinoline derivatives by using microwave irradiation with reduced reaction times in good yields using readily available starting materials excluding ethoxymethylene derivatives. The study also supersedes the old wet classical methodologies by microwave assisted multi component one pot synthesis. Further, this study also shows some limitations in the said reaction for the cyclization of the molecule at possible positions (as in case of *meta*-substituted aryl amines) and also explores the effect of solvent in the last step.

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