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COMPARATIVE SYNTHESIS AND PHYSICOCHEMICAL CHARACTERIZATION OF SUBSTITUTED 2-METHYLQUINOLIN- 4(IH)-ONE BY VARIOUS CONVENTIONAL AND MICROWAVE METHODS

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Microwave, Catalytic, Substituted quinolone, Cyclisation agents

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ABSTRACT: In the present work various conventional methods and microwave method for synthesis of substituted quinolone reported. Substituted anilines were taken as a starting material and reacted with ethyl acetoacetate in presence of catalytic amount of acid and cyclized by various cyclisation agents that give the title compounds which differ in its color intensity, reaction time as well in % yield. Based on results we obtain, it has been concluded that microwave method for synthesis of substituted quinolone is more convenient in terms of reaction time and use of solvent.

INTRODUCTION: The quinolones are a class of bicyclic molecules, organic chemical structures that are related to the heteroaromatic coal tar isolate quinoline. Specific quinoline molecules substituted with a hydroxyl functional group at carbons 2 and 4 (C-2 and C-4) are most often observed in isomeric forms termed 2- and 4-quinolones, respectively. The relative importance of 4-quinolones has increased with the discovery that such structures that also bear a carboxylic acid (-COOH) and other functional groups at particular sites on the ring have very potent antimalarial activity, inhibiting cytochrome bc₁ complex of *Plasmodia* leads to inhibition of respiration and potent bactericidal activities, inhibiting of a broad spectrum of Gram negative and Gram positive DNA gyrase and topoisomerase enzymes.

Hence, they are very useful in antibacterial therapy. An example of such a 4-quinolone is ciprofloxacin, where the atoms of quinoline can be traced within this related structure. Ciprofloxacin is a "second-generation" fluoroquinolone antibacterial, introduced by Bayer AG and still in wide use as the second decade of the new millennium begins.

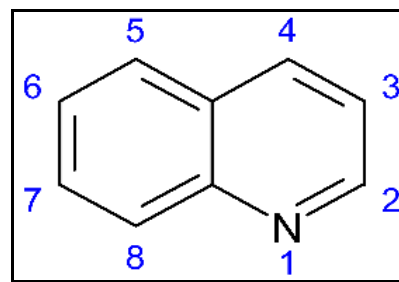


FIGURE 1: THE COAL TAR-DERIVED PARENT HETEROCYCLIC ORGANIC MOLECULE QUINOLINE, SHOWN WITH ITS ACCEPTED NUMBERING SCHEME TO INDICATE SITES OF SUBSTITUTION

In the chemical synthesis of specific quinolines, the nitrogen-containing ring is often "closed" as a part of the synthetic process, and in some syntheses,

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doing so can install an hydroxyl group (an –OH functional group) on carbons adjacent to or across from the ring nitrogen (i.e., the C-2 and the C-4 positions, see quinoline structure above). An example of such a synthesis is the Camps cyclization, which, depending on exact starting materials and reaction conditions, can give both 2-hydroxyquinolines (**B**) and 4-hydroxyquinolines (**A**) as shown.

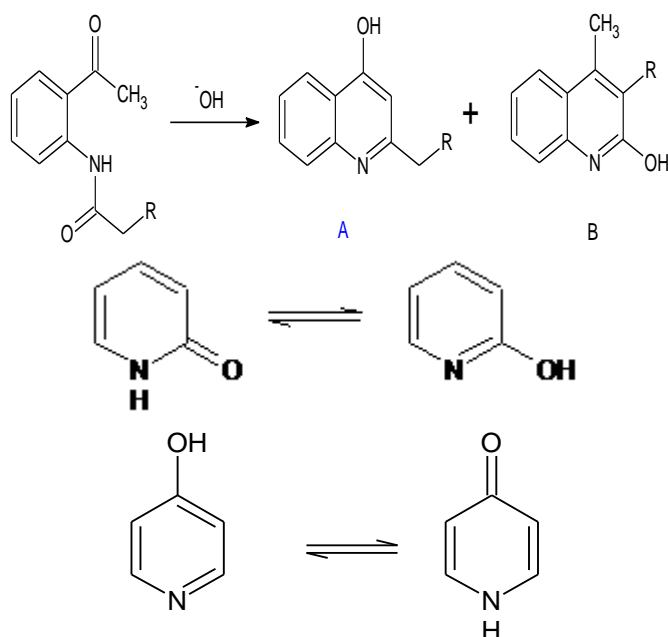


FIGURE 2: TAUTOMERIZATION OF NITROGEN-CONTAINING PYRIDINE RING OF 2- AND 4-HYDROXY - SUBSTITUTED QUINOLINE HETEROCYCLES

The tautomerization of nitrogen-containing pyridine ring of 2- and 4-hydroxy-substituted quinoline heterocycles images, that leads to corresponding carbonyl-containing isomers (tautomers). Here, the adjacent all-carbon aromatic ring of quinoline is omitted to emphasize the local changes in proton and double bond positions during the tautomerization. Note that the order of the tautomers alternates between the two schemes.

Such hydroxy-substituted quinolines are, most often, not distinguished from a particular isomeric form termed a tautomer. In this particular rapid isomerization, the labile proton (H^+) migrates from the hydroxyl group to the ring nitrogen, and the double bond (π -electron density) migrates from within the ring to the carbon-oxygen bond to form a carbonyl group. These tautomerizations are represented in the images at right by the same

process in closely related structures. (The tautomerizations also take place when the adjacent all-carbon ring is absent.) When represented as the carbonyl-containing tautomer—often the most stable form, so the one observed in structure measurements such as room temperature NMR—the pair of hydroxy-substituted quinolines shown above are formally referred to as 2-quinolones (oxygen adjacent to the ring N) or 4-quinolones (oxygen across from the ring N), as the case may be.

Quinolones and quinoline derivatives are a major class of alkaloids and have remarkable applications in the field of medicinal chemistry. Quinolones are known to possess cytotoxic, antimetabolic, antibacterial and anti-platelet properties and some serve as cardiovascular protectors.

Classical methods for the synthesis of 2-methyl-4-quinolones and their derivatives 3-quinolones and their quinoline derivatives can be interconverted through oxidation and reduction reaction (**Fig. A**). The 2-methyl-1, 2, 3, 4-tetrahydroquinolin-4(1H)-ones ($R^2=H$) **A** can be transformed into the corresponding 2-methylquinolin-4(1H)-ones **B** with unsaturation between C2- C3 position. The latter, in turn, can be converted to fully aromatic quinoline derivatives **C**. Several methods have been developed for the direct oxidation of system **A** to **C**.

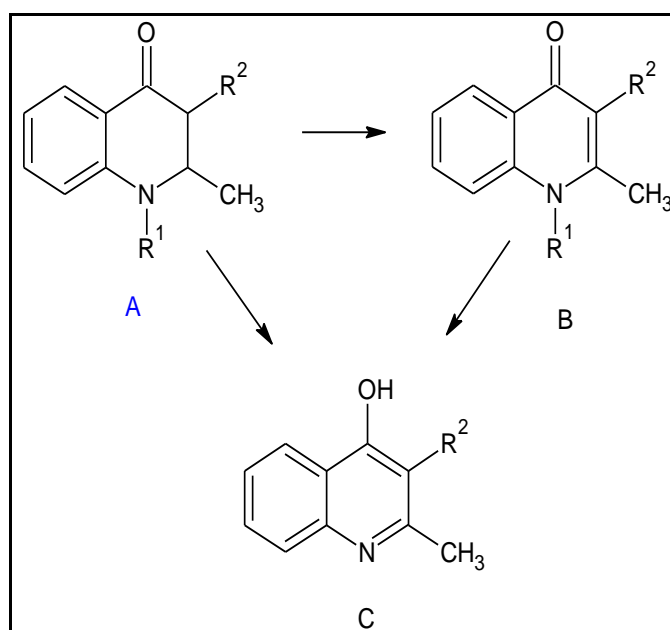
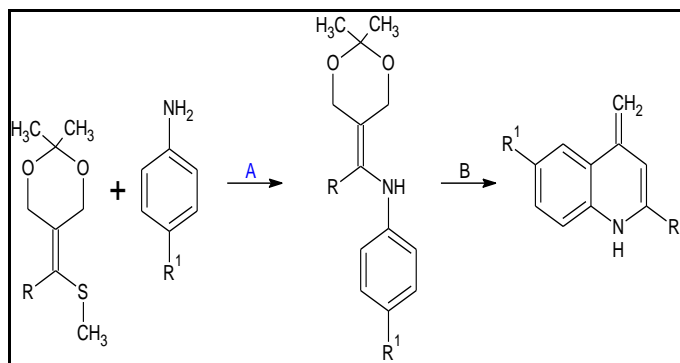


FIGURE 3: INTERCONVERSION OF QUINOLONES AND THEIR DERIVATIVES THROUGH OXIDATION AND REDUCTION REACTIONS

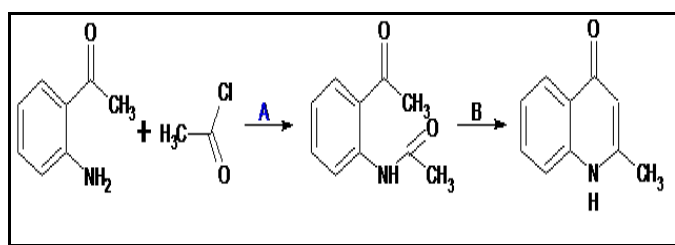
There are several pathways described in literature for the preparation of 2-methyl-4(1*H*)-quinolone. The reaction of 2, 2-dimethyl-5-methylthioalkylidene-1, 3-dioxane-4,6-diones with aryl amine in diphenyl ether without isolating intermediate.



R1 = H, -CH3, -NO2, -Br, -Cl; R = -CH3, Ar
Reaction Condition: (A) (C6H5)2O, 1400C, 30min or C2H5OH, heat. 2-4hr. (B) (C6H5)2O, 250-2600C. N2(g)

SCHEME-1

The most convenient method reported to date for the synthesis of 2-methyl-4(1*H*)-quinolone involves the use of 2-aminoacetophenones and acetyl chloride as starting materials.



Reaction Condition: (A) NEt3, THF, 00C to r.t, 2 hr. (B) t-BuOK, t-BuOH, heat, 20 h

SCHEME-2

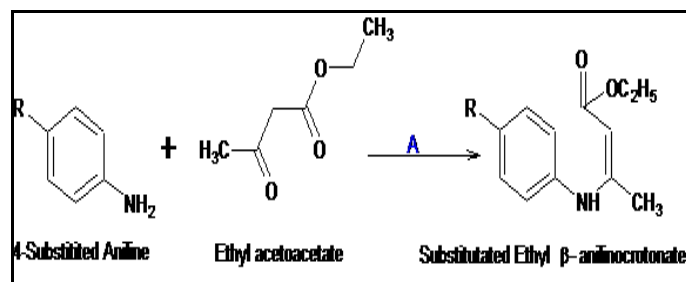
Experimental

General Procedure: Preparation of Substituted 2-Methylquinolin-4(1*H*)-ones using Biphenyl ether as a cyclisation agent⁴⁻⁷

Quinolin-4(1*H*)-ones were prepared by using one of the standard procedures for Conrad-Limpach reaction. An oven-dry 100mL round-bottom flask attached to a Dean-Stark trap equipped with a reflux condenser was charged with a substituted aniline (0.25mol), ethyl acetoacetate (0.25mol), benzene (25 mL), and glacial acetic acid (1 mL). The mixture was heated at 100°C until no more water was separated (3-24 h). The benzene was distilled under reduced pressure, and the resulting enamine was then used in the next step without

further purification. Biphenyl ether (30 mL) was stirred and heated at reflux, while enamine was added rapidly through the dropping funnel. Stirring and refluxing continued for 10-15 min until no more ethanol separated within the Dean-Stark trap. The mixture was then allowed to cool to room temperature while precipitation arose. The solid was filtered off and washed with hexane and acetone. Ice cold methanol washing may be necessary in some cases. No further purification was needed. The yield is reported over the two steps.

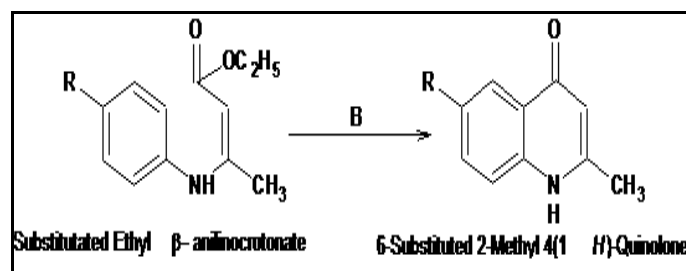
STEP-1



R = -H, -OCH₃

Reaction Condition: (A) R-aniline, AcOH, benzene, Dean-Stark trap, reflux overnight

STEP-2



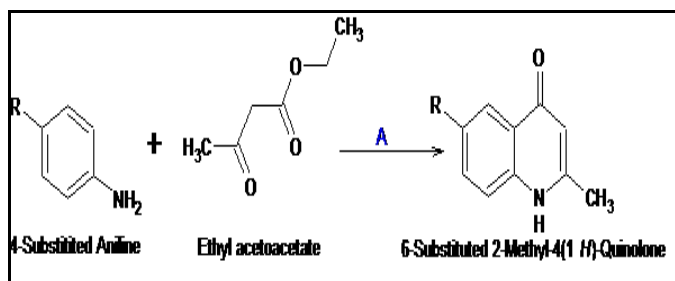
R = -H, -OCH₃

Reaction Condition: (B) Ph₂O, reflux, 15 min

General Procedure: Preparation of Substituted 2-Methylquinolin-4(1*H*)-ones using Sulphuric acid as a cyclisation agent⁸

Quinolin-4(1*H*)-ones were prepared by using one of the standard procedures for Conrad-Limpach reaction. An oven-dry 100mL round-bottom flask attached to a reflux condenser was charged with a substituted aniline (0.25mol), ethyl acetoacetate (0.25mol), dioxane (20 mL), and trace of HCl. The mixture was heated at 70-80 °C for 3-4 hr., cooled at room temperature and conc. Sulphuric acid (20ml) was added. Then the mixture was refluxed at 190-200°C for 1 h and hot mixture was poured in 500mL of ice cold water with constant stirring.

Separated solid was filtered, dried, and recrystallized from ethanol.

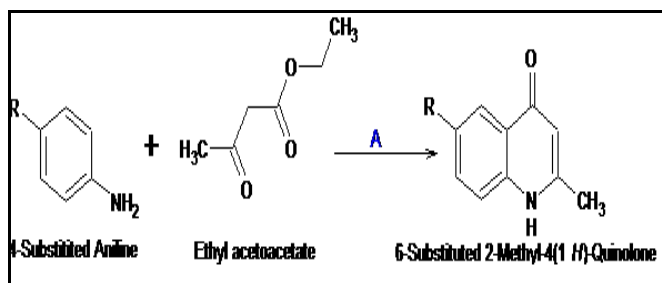


R = -H, -OCH₃

Reaction Condition: (A) R-aniline, trace of HCl, dioxane, reflux for 3-4 hr. then Conc. H₂SO₄, reflux for 30-40 min.

General Procedure: Preparation of Substituted 2-Methylquinolin-4(1H)-ones using Sulphuric acid as a cyclisation agent⁹⁻¹¹

Quinolin-4(1H)-ones were prepared by using one of the standard procedures in which polyphosphoric acid acts as dual agent like condensing as well cyclisation. An oven-dry 100mL round-bottom flask attached to a reflux condenser was charged with a substituted aniline (0.25mol), ethyl acetoacetate (0.25mol), dioxane (20 mL), and polyphosphoric acid (85% P₂O₅) (1mol). The mixture was heated on water bath for 2-3 hr., cooled at room temperature and mixture was poured in 400mL of ice cold water with constant stirring. Separated solid was filtered, dried, and recrystallized from ethanol.



R = -H, -OCH₃

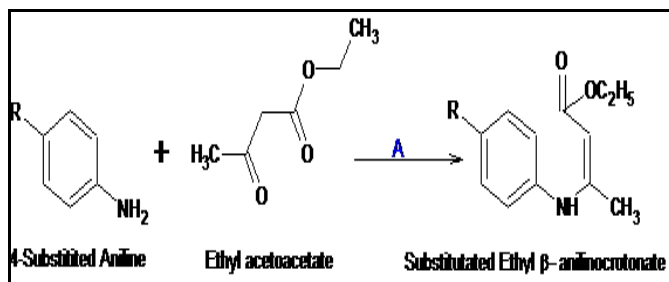
Reaction Condition: (A) R-aniline, dioxane, polyphosphoric acid (85% P₂O₅), heat on water bath for 2-3 hr.

General Procedure: Preparation of Substituted 2-Methylquinolin-4(1H)-ones using Microwave¹²⁻¹⁷

Preparation of β - anilincrotonates from substituted aniline:

0.1 mole substituted aniline and ethyl acetoacetate were mixed and 5-10 drops of Conc.HCl was added and the mixture was shaken well. It was left aside

for few minutes and the mixture became turbid indicating the liberation of water due to the condensation reaction. At this stage, the mixture was kept inside a vacuum desiccator over Conc.H₂SO₄ and was kept as such for 2-3 days, thereafter the ethyl- β -anilincrotonates which formed as a deep yellow oily liquid, was separated, dried over anhydrous sodium sulphate and used for the subsequent cyclization reaction.

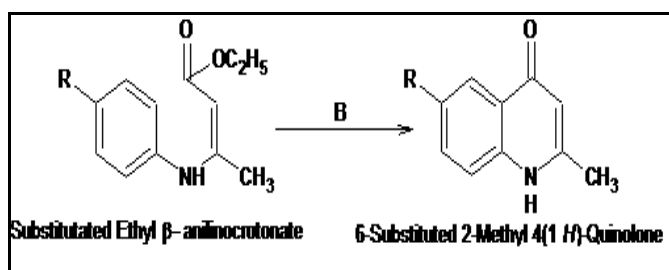


R = -H, -OCH₃

Reaction Condition: (A) HCl, R.T., for 2-3 days

Synthesis of Quinolone from β anilincrotonates:

Ethyl β - anilincrotonates was introduced under microwave heating for 3 min at 360W. The solid formed was washed with hexane and then washing was continued with a mixture of chloroform and petroleum ether (30:10). The pure powder was taken for analysis and further reaction.



R = ELQ-1 = -H, ELQ-2 = -OCH₃

Reaction Condition: (B) Microwave 360 W, 3 min, Neat condition

Characterization of Compounds:

2-methylquinolin-4(1H)-one (ELQ-1)

Compound ELQ-1 was prepared following modified general procedure 4. The precipitate was collected, washed with hexane, and recrystallized from ethanol to give 92% yield as a white solid.

M.P = 238-240 °C

IR = 2990 (aromatic C-H), 1648 (-C=O)

MS= M⁺ 160.09(M⁺), 161.1

6-methoxy-2-methylquinolin-4(1H)-one (ELQ-2)
Compound Shy-2 was prepared following modified general procedure 4. The precipitate was collected, washed with hexane, and recrystallized from ethanol to give 88-90% yield as a brown-white solid.

M.P = 200-201°C

IR = 2950 (aromatic C-H), 1638 (–C=O), 1179 (–OCH₃)

MS = 190.09 (M⁺), 192.2

RESULTS AND DISCUSSION:

Synthetic Chemistry

Previously, various synthetic methodology for synthesis of 4(1H)-Quinolone has been reported by various researchers. Conrad and Limpach 1887, reported the synthetic procedure using biphenyl

ether as a cyclisation agent. But the limitation of this method is long reaction time and very low yield. So various researchers have done cyclisation of initial step using different cyclisation agents to overcome the previous limitations. Gupta et al 2011, reported the synthetic methodology using Conc. H₂SO₄ as cyclisation agent. But again there is limitation of charring of final compound because of high reaction temperature of cyclisation step. So, overcome this limitations various researchers have reported the synthesis of 2-Alkyl-4quinolone and 2-Alkyl-4-methoxyquinoline using microwave. So it is thought of interest to develop synthetic methodology for 4(1H)-Quinolone using microwave. As per different experimental conditions results are given in below **Table 1** and **2**.

TABLE 1: RESULTS OF COMPARISON OF CONVENTIONAL AND MICROWAVE METHODS FOR SYNTHESIS OF 2-METHYLQUINOLIN-4(1H)-ONE

Parameters	Cyclization Agent			
	Biphenyl Ether	Conc.H ₂ SO ₄	Polyphosphoric acid	Microwave
Color of crude product	Yellow	Brown	Buff white	Off white
Melting point(°C) of crude product	232-234	231-233	234-236	238-240
% yield	60	50	55-57	92
Melting point(°C) of recrystallize product	238-240	237-239	238-241	238-240
R _f Value	0.65	0.65	0.65	0.65
Reaction time	25 hr.	8 hr.	5-6 hr.	4-6 min.

Mobile phase: Chloroform: Methanol (2:1)

TABLE 2: RESULTS OF COMPARISON OF CONVENTIONAL AND MICROWAVE METHODS FOR SYNTHESIS OF 6-METHOXY 2-METHYLQUINOLIN-4(1H)-ONE

Parameters	Cyclization Agent			
	Biphenyl Ether	Conc.H ₂ SO ₄	Polyphosphoric acid	Microwave
Color of crude product	White yellow	Dark brown	White brown	Off white
Melting point(°C) of crude product	195-197	194-197	198-200	200-201
% yield	55	45	50	88-90
Melting point(°C) of recrystallize product	199-201	198-200	199-202	200-201
R _f Value	0.71	0.71	0.71	0.71
Reaction time	25 hr.	8-9 hr.	4-5 hr.	4-6 min.

Mobile phase: Chloroform: Methanol (2:1)

CONCLUSIONS: After performing all these relevant experiments, among the conventional methods Polyphosphoric acid is better cyclizing agent as it gives better product. It has been concluded that Microwave method is best for the synthesis of quinolone because it is less time

consuming, cheap as it is solvent free and gives high yield.

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