Ain Shams University
Faculty of Education
Department of Chemistry

Synthetic Utility of Some Substituted Quinolinones

A Thesis Submitted
By

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In partial Fulfillment for
Requirements of Master Degree for Teacher's Preparation in Science (Organic Chemistry)

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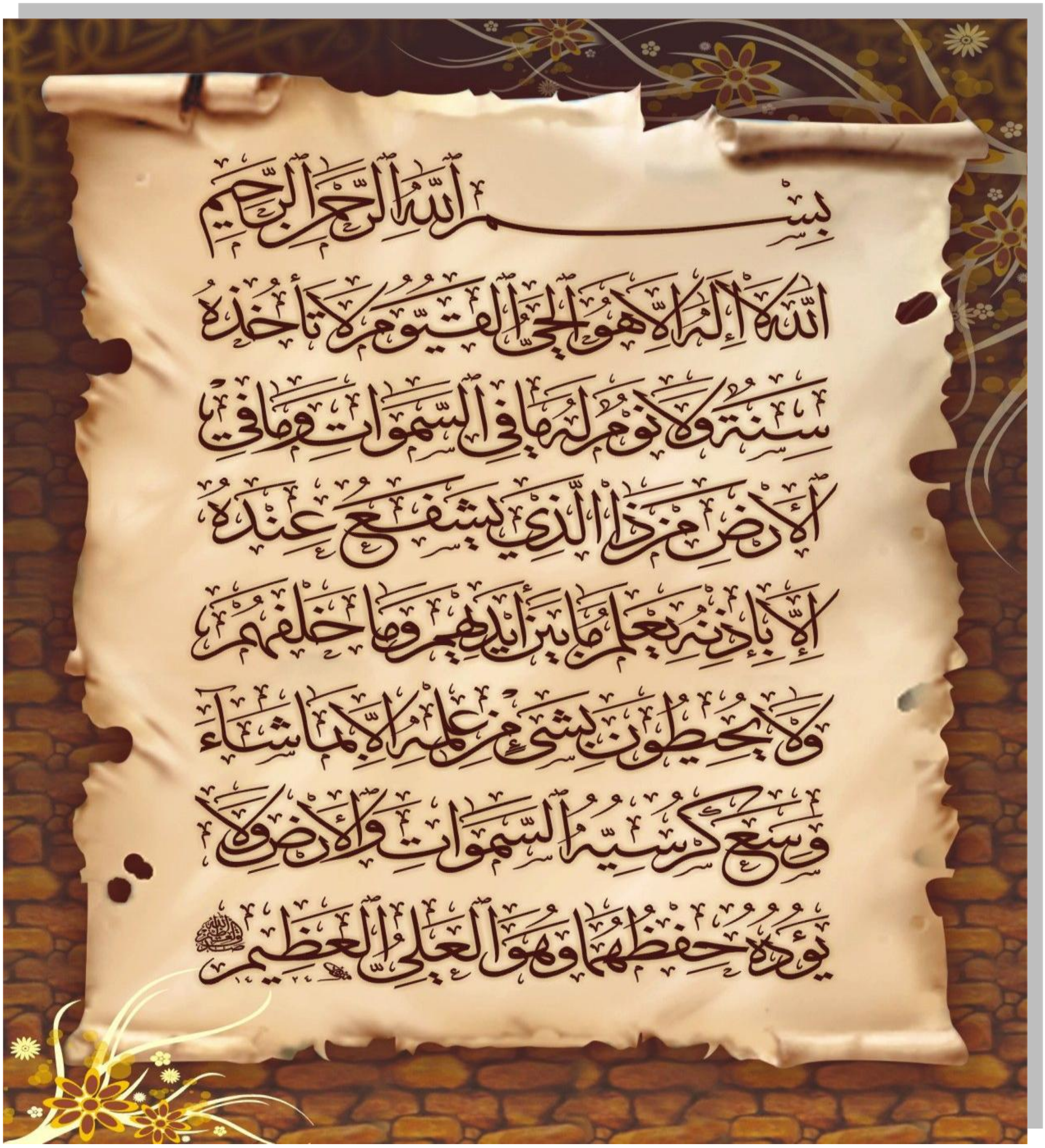
بسم الله الرحمن الرحيم
الله لا إله إلا هو الحي القيوم لا تأخذه
سنة ولا نوم له ما في السموات وما في
الأرض من ذا الذي يشفع عنده
إلا بإذنه يعلم ما بين أيديهم وما خلفهم
ولا يحيطون بشيء من علمه إلا بما شاء
وسع كرسيه السموات والأرض ولا
يؤده حفظهما وهو العلي العظيم

First of all, deep and grateful thanks
come from all my heart to Allah
For offering me
Great parents
Pretty sister
Smart brother & his wife
and lovely Hassan

Ain Shams University
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Department of Chemistry

Approval Sheet

Synthetic Utility of Some Substituted Quinolinones

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Higher studies:

The thesis was approved Approval date / / 2013

Approved by Council of Faculty Approved by Council of University

Date / / 2013 Date / / 2013

Theoretical Studies

The Student had successfully studied the following Programs and courses:

1. General Diploma for Teacher's Preparation in Science (Chemistry):

i. Organic Chemistry 1: Natural Products and Polymer Chemistry
ii. Organic Chemistry 2: Reaction Mechanism and Stereochemistry
iii. Physical Chemistry 1: Catalysis Chemistry and Electrochemistry
iv. Physical Chemistry 2: Quantum Chemistry
v. Inorganic Chemistry 1: Polarography
vi. Inorganic Chemistry 2: Organometallic Compounds
vii. Inorganic Chemistry 3: Chemistry of Solutions
viii. Inorganic Chemistry 4: Metal Chelates
ix. Educational Course I
x. Educational Course II
xi. English Language

2. Special Diploma for Teacher's Preparation in Science (Organic Chemistry):

i. Organic Chemistry 1: Spectroscopy I: IR, UV and Mass Spectrometry
ii. Organic Chemistry 2: Spectroscopy II: NMR Spectrometry
iii. Organic Chemistry 3: Chemistry Heterocyclic Compounds
iv. Organic Chemistry 4: Selected Topics: Aromaticity, Tautomerism and, Delocalized Chemical bonding.
v. Organic Chemistry 5: Stereochemistry
vi. Organic Chemistry 6: Organic Reactions
vii. Organic Chemistry 7: Free Radicals Reactions
viii. Organic Chemistry 8: Sulfur and Phosphorus and Organic Analytical Chemistry
ix. Organic Chemistry 9: Review Article
x. Educational Course I
xi. Educational Course II
xii. English Language

3. Master Degree for Teacher's Preparation in Science (Organic Chemistry):

i. Organic Chemistry 1: Physico-Organic Chemistry
ii. Organic Chemistry 2: Microanalysis and Modern Organic Synthesis
iii. Organic Chemistry 3: Advanced Organic Spectroscopy
iv. Organic Chemistry 4: Pericyclic Reactions
v. Educational Course I
vi. Educational Course II
vii. English Language

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Heba Hassan Ibrahim

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Table of Abbreviations

Abbreviation	Expression
Ac	Acetyl (CH_3CO)
Ar	Aromatic or aryl group
as	Asymmetric
aq.	Aqueous
^{o}C	Celsius
$CDCl_3$	Deuteriochloroform
^{13}C NMR	Carbon-13 nuclear magnetic resonance
D_2O	Deuterium monoxide
DMAP	4-(N,N-dimethylamino)pyridine
DMF	Dimethylformamide
DMF-DMA	Dimethylformamide-dimethylacetal
DMSO	Dimethylsulfoxide
DMSO-d_6	Hexadeuterio dimethylsulfoxide
DNA	Deoxyribonucleic acid
DPPH	α,α-diphenyl-β-picrylhydroxyl radical
DTG	Derivative thermogravimetric curve
DSC	Differential scanning calorimetry
en gl	Ethylene glycol
eV	electron Volt
FT-IR	Fourier transform infrared spectroscopy
g	gram (mass unit = 0.001 Kg)
G –ve	does not retain crystal violet dye by Gram staining
G +ve	stains dark blue or violet by Gram staining
8OHDG	8-hydroxy-2'guanosine
^{1}H NMR	Proton nuclear magnetic resonance
h	Hour
WHO	World health organization
±I	Inductive effect (withdraw or repulse)
IC_{50}	Concentration causing 50% inhibition
IR	Infrared spectrum
I_r %	Intensity ratio (relative to base peak ion)
in situ	In position (Latin)
in vitro	In glass (Latin)
in vivo	Within the living (Latin)
J	Coupling constant (Hz) in NMR measurements
L-proline	Pyrrolidine-3-carboxylic acid
M	Molar (Molarity)
±M	Mesomeric effect (withdraw or repulse)
m.p. (T_m)	Melting Point
MW	Microwave assisted process
M.Wt.	Molecular weight
m/z	Mass to electron charge ratio
mL	Milli-liter
MDA	Malondialdehyde
MHz	Mega Hertz
MIC	Minimum inhibitory concentration
MS	Mass spectrum

Abbreviation	Expression
NBS	N-Bromosuccinimide
nm	nanometer
NMDA	N-Methyl-D-aspartate
NMP	N-Methylpyrrolidone
PPA	Polyphosphoric acid
PTC	Phase transfer catalysis
PZQ	Praziquantel (drug of Bilharzia)
ROS	Reactive oxygen species (oxidants)
RNS	Reactive nitrogen species
rt	Room temperature
TB	Tuberculosis
TBAB	Tetrabutylammonium bromide
T_c	Crystallization temperature
TEA	Triethylamine
TEG	Triethylene glycol
TfOH	Trifluoromethanesulfonic acid (triflic acid; CF_3SO_3H)
TGA	Thermal gravimetric analysis
THF	Tetrahydrofuran
T_m	Melting point temperature
TMS	Tetramethylsilane
Ts	*p*-Toluenesulfonyl
TLC	Thin layer chromatography
UV	Ultraviolet
X-ray	electromagnetic radiation (wavelength 0.01 to 10 nm)
Δ	Heat
δ	Chemical shift
λ	Wave length
ν	Wave number

Aim of the work

In this research work, we aimed to:

1. Study of *Riley* oxidation reaction of 1-alkyl-3-acetyl-4-hydroxyquinolin-2(1*H*)-ones, at different reaction conditions.
2. Investigate the chemical behavior of α-keto acid towards different reagents and conditions.
3. Utilize of α-keto acid and/or its esters as synthons
4. Synthesize of quinolinones bearing different nitrogen heterocycles in one molecular frame which are expected to be bioactive compounds.
5. Compare the chemical behavior of α-keto acids and α-keto esters towards some nucleophiles.
6. Study of some physical properties for certain selected new products such as Thermal studies; DSC, TGA, and photolysis.
7. Evaluate biological activity of some new substituted quinolinone products, as antimicrobials, antitumors, antioxidants and antiparasites.

Abstract

Synthetic Utility of Some Substituted Quinolinones

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Oxidation of 3-acetyl-1-alkyl-4-hydroxyquinolin-2(1*H*)-ones, *via Riley* reaction using selenium dioxide, produced a mixture of α-keto acids and their dehydrated dimer derivatives. The oxidation reaction conditions were optimized through variation of the reaction molar ratios, solvent, additives, and time. Also 3-(2-nitroacetyl)quinolinones and 3-acetyl-4-(difluoroboryloxy)quinolinones were subjected to this oxidation reaction, in which boron-complex revealed selectivity to α-keto acids. Alkaline degradation of dimers led to formation of the 4-hydroxy-2-oxoquinoline-3-carboxylic acids while under the same conditions α-keto acids underwent deoxalylation. α-Keto acids were esterified to give the corresponding α-keto esters. Thermolysis and acidic and alkaline hydrolysis of α-keto acids were studied as well as halogenation under different conditions. The chemical behavior of both of α-Keto acids and esters was studied towards different nucleophiles, such as; amines, hydrazines, semicarbazides, and active methylene compounds to afford novel quinolinone derivatives bearing heterocyclic substituents, such as triazines. DSC and TGA thermal studies of some selected new products were carried out revealing their thermal stabilities. Certain new substituted quinolinone products were screened for their biological activity in which some products indicated significant antimicrobial, antitumor, antioxidant and antiparasitic activities.

Keywords: oxidation, selenium dioxide, quinolinone, α-keto acid, heterocyclization, thermal analysis, biological applications

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Summary

Synthetic Utility of Some Substituted Quinolinones

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This research work focused on oxidation 3-acetyl-1-alkyl-4-hydroxyquinolin-2(1*H*)-ones in order to utilize the oxidized product in preparation some new derivatives of quinolinone. These derivatives were targeted due to their expected biological applications. The chemical and spectral properties were studied as well as the effect of some selected products against bacteria, fungi, tumors and parasites have been screened.

3-Acetyl-1-alkyl-4-hydroxyquinolin-2(1*H*)-ones were subjected to the known *Riley* oxidation, using selenium dioxide in refluxing dioxane, to give two unexpected products; 2-(1-alkyl-4-hydroxy-2-oxo-1, 2-dihydroquinolin-3-yl)-2-oxoacetic acids **5a,b** and 1'-alkyl-2-(1-alkyl-2,4-dioxo-1,2-dihydroquinolin-3(4*H*)-ylidene)-1'H-spiro-[pyran-4,3'-quinoline]-2',3,4',5,6(2*H*)-pentanones **6a,b** (R = CH_3, C_2H_5). Furthermore, the oxidation reaction of these two acetyl derivatives **1a,b** was carried out under different molar ratios of the reagent, selenium dioxide. It was observed that duplicate amount of selenium dioxide gave the highest yield of α-keto acids **5a,b**. Studying of the effect of the reaction solvent revealed that boiling dioxane can be the solvent of choice which leads to the highest yield percentage of α-keto acids **5a,b.** The inspection of the proper reaction time showed that four hours are enough to get the highest yield. The effect of various additives showed that presence of nitric acid may improve the yields while presence of other acids or bases as well as presence of water diminished the yields. As a result of this reaction study it is concluded that the reaction's optimum conditions are: usage of dry dioxane at boiling, molar ratio of acetyl derivative/selenium dioxide is 1:2 and reaction time is four hours.