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Manzoor Ahmad Shah
M. Phil Scholar, Noida International University, Uttar Pradesh, India

Dr. Abhilekha Sharma
Asst. Prof, Department of Chemistry, Noida International University, Uttar Pradesh, India

Corresponding Author:
Manzoor Ahmad Shah
M. Phil Scholar, Noida International University, Uttar Pradesh, India

Synthesis of Quinoline-Thiazole Compound (Ethyle 2-Chloroquinoline-3-yl) Methylene amino)-4-methylthiazole-5-carboxylate)

Manzoor Ahmad Shah and Dr. Abhilekha Sharma

Abstract
Compounds classified as heterocyclic probably constitute the largest and most varied family of organic compounds, every Carbo-cyclic compound, regardless of structure and functionality may in principle be converted into a collection of heterocyclic analogs by replacing one or more of the ring carbon atoms with a different element.
Quinoline is a heterocyclic aromatic organic compound with the chemical formula C9H7N. It is a colorless hygroscopic liquid with a strong odor. Aged samples, especially if exposed to light, become yellow and later brown. Quinoline is only slightly soluble in cold water but dissolves readily in hot water and most organic solvents.
Quinoline-Thiazole compound have been prepared by the reactions of different chemical compounds. First aniline reacts with acetyl chloride to give acetanilide. Acetanilide undergoes Vilsmeier reaction by involving use of DMF and POCl3 to give aldehyde. Ethyl acetoacetate on the other hand reacts with THF and Thiourea to yield Thiazole. Aldehyde then reacts with the Thiazole in presence of glacial acetic acid to give the desired compound.

Keywords: Thiazole, Quinoline, Heterocyclic, NMR, IR, Mass spectrum etc

Introduction
Quinoline antimicrobials represent an example of drugs with improved pharmacodynamics and safety. Nalidixic acid, the first drug of this class, was active only against Gram-negative bacteria, and its use was limited to urinary tract infections because it achieves only low blood concentrations and poor tissue distribution, and was metabolized rapidly in the human body. In contrast, Norfloxacin, which came to market in 1984, maintains a stable metabolic state and exhibits good tissue distribution. Its antimicrobial spectrum is extensive, covering both Gram positive and Gram-negative bacteria including P. aeruginosa.
Quinoline antimicrobials developed after Norfloxacin have been called new Quinolines, and they have still been key drugs. Levofloxacin is the S-(+) enantiomer of the new Quinoline ofloxacin. This enantiomer has higher antimicrobial activity than that of the other R-(-) enantiomer of ofloxacin, and is associated with weaker side effects on the central nervous system, such as restlessness and vertigo. Although a large number of companies in various countries have competed in the development of newer antimicrobial agents, the number of brand new drugs has been remarkably decreasing in recent years, with few antimicrobial agents of new classes becoming available.
Quinoline is a heterocyclic aromatic organic compound with the chemical formula C9H7N. It is a colorless hygroscopic liquid with a strong odor. Aged samples, especially if exposed to light, become yellow and later brown. Quinoline is only slightly soluble in cold water but dissolves readily in hot water and most organic solvents. Quinoline itself has few applications, but many of its derivatives are useful in diverse applications.
A prominent example is quinine, an alkaloid found in plants. 4-Hydroxy-2-alkylquinolines (HAQs) are involved in antibiotic resistance.
Quinoline is the simplest member of the Quinoline class of compounds, comprising a benzene ring Ortho fused to C-2 and C-3 of a pyridine ring. It is a Mancude organic hetero bi cyclic parent, a member of Quinolines, a Nazarene and an Ortho-fused Heteroarene.

Compounds classified as heterocyclic probably constitute the largest and most varied family of organic compounds, every carbo-cyclic compound, regardless of structure and functionality may in principle be converted into a collection of heterocyclic analogs by replacing one or more of the ring carbon atoms with a different element. Even if we restrict our consideration to oxygen, nitrogen and sulfur (the most common heterocyclic elements), the permutations and combinations of such replacements are numerous.

Methodology and materials

1. Reagents and chemicals used: Aniline derivatives, POCl3, EtOAc, Hexane, THF, Ethylaceto Acetate, Ethanol, Methanol, DCM, DMF, glacial acetic acid, Zn dust, NBS, 70% Acetic acid.

All the reagents and chemicals were procured from Qualigens, LOBA Chemie Pvt. Ltd. and CDH. All the compounds procured were purified and dried, whenever necessary before use, following standard methods.

2. Apparatus used: Beakers, test tubes, glass rods, magnetic stirrer, thermometer, round bottom flask, reflux condenser, iodine flasks, watch glass, conical flasks, burette, Measuring cylinders, Buchner Funnel, droppers and pipettes.

3. Analytical work: 1) Melting point was determined by using melting point apparatus, Noida International University.

2) Reactions were monitored by thin layer chromatography (TLC) on a pre- coated silica gel G plated using Iodine vapor, Ninhydrin and DNP as visualizing agent.

3) IR spectra were recorded on JASCO FTIR-420.

NMR spectra were recorded on Bruker AVANCE III 600MHz NMR spectrometer. Mass spectra were recorded on JEOL GCMATE II MS spectrometer was recorded at Central Instrumentation Facility Jamia Milia Islamia Delhi, Jamia Nagar New Delhi.

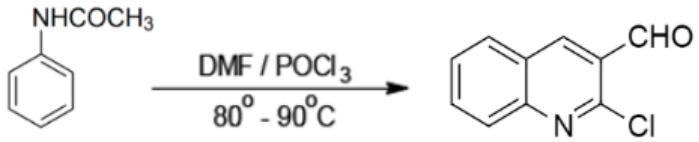
Step 1: Synthesis of acetanilides

A mixture of aniline (0.11mol) and Zn dust were added to acetic acid (1mol) in a 100ml round bottom flask, and heated over a gentle flame using water condenser. Heating was continued for about 2hrs. The reaction mixture was then carefully poured in water (100ml) in 250ml beaker with cooling and stirring. The shining crystals of their corresponding acetanilide were separated slowly. After 15mins the corresponding acetanilide crystals were collected by filtration. The solid crystals were washed over Buchner funnel with water and product was dried

Aniline Acetyl chloride Acetanilide

Step 2: Synthesis of 2-chloro-3-Carbaldehyde Quinolines

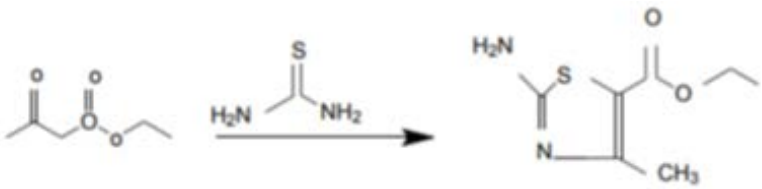
The compound was prepared from acetanilide under Vilsmeier - Hack reagent (POCl3/DMF).To a solution of acetanilide (1mol) in DMF (3mol) with stirring POCl3 was added drop wise. The reaction mixture was stirred at 80-90 ℃ for time ranging between 4-16hr. This mixture was poured in crushed ice, stirred for 5mins where corresponding 2-chloro-3-formyl Quinolines formed was filtered, washed well with water and dried. The compounds were purified by recrystallization from either ethyl acetate or acetonitrile. 2-chloro-3-Cabaldehyde Quinoline.



Acetanilide 2-Chloroquinoline-3-Carbaldehyde

Step 3: Synthesis of Ethyl 2-amino-4-methylthiazole-5-carboxylate

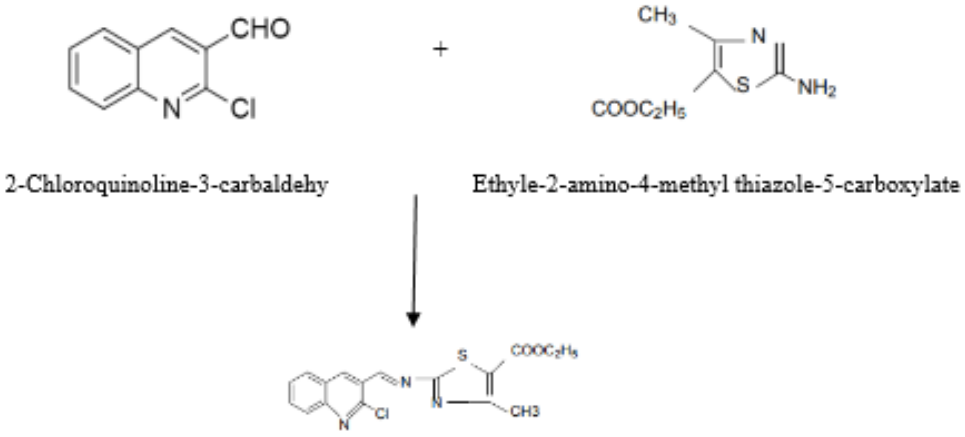
To a mixture of ethyl acetoacetate in water (50.0 ml) and Tetra hydro Furane add NBS (0.06mol). The reaction mixture was stirred at room temperature for 2 hours and Thiourea 10gm was added and the reaction mixture was heated to 80 ºC for 2 hrs after cooling to room temperature the reaction mixture was filtered to get rid of the insoluble substances, then NH3H2O was added to the filtrate. The resulting yellow floccules were stirred at room temperature for 10 minutes and filtered. The filtrate cake was washed with water and recrystallized with ethyl acetate, then dried to get the target compound.



Ethyl acetoacetate Ethyle-2-amino 4 methyl thiazole-5-carboxylate

Step 4: Synthesis of 2-Chloroquinoline-3yl-methyleneamine-4-methyl thiazole-5-carboxylate.

A mixture of aldehyde and Thiazole was refluxed in methanol (30ml) on a water bath for 6 hrs. The reaction contents were cooled to room temperature and workup done with water. The resulting solid was filtered, washed with sodium sulphate solution then with water, dried and recrystallized from ethanol to give the target compound.



Ethyl 2-Chloroquinoline-3-yl) methylene amino)-4-methylthiazole-5-carboxylate

Results and Discussions

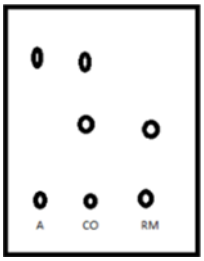
Preparation of acetanilide

A mixture of aniline (0.11mol) and Zn dust were added to acetic acid (1mole) in a 100ml round bottom flask, and heated over a gentle flame using water condenser. Heating was continued for about 2hrs.The reaction mixture was then carefully poured in water (100ml) in 250ml beaker with cooling and stirring. The shining crystals of their corresponding acetanilide were separated slowly. After 15mins the corresponding acetanilide crystals were collected by filtration. The solid crystals were washed over Buchner funnel with water and product was dried.

Yield: 80% (M + H+) = 135

Melting Point = 114 ºC

Reaction progress checked with TLC (7:3) Chloroform: Hexane



T.L.C

A = Aniline, Co = Aniline + RM, RM = Reaction mixture

Preparation of Quinoline aldehyde

The compound was prepared from acetanilide under Vilsmeier - Hack reagent (POCl3/DMF). To a solution of acetanilide (1mol) in DMF (3mol) with stirring POCl3 was added drop wise. The reaction mixture was stirred at 80-90° C for time ranging between 4-16hr. This mixture was poured in crushed ice, stirred for 5mins where corresponding 2-chloro-3-formyl Quinolines formed was filtered, washed well with water and dried. The compounds were purified by recrystallization from either ethyl acetate or acetonitrile.

Yield = 70% (M + H+) = 191

Melting point = 149 ºC

Isolated compound submitted for 1HNMR

1H NMR (DMSO): δ 10.3(1H), δ 8.98(1H), δ 8.27(1H), δ 8.00(1H) and δ 7.76(1H)

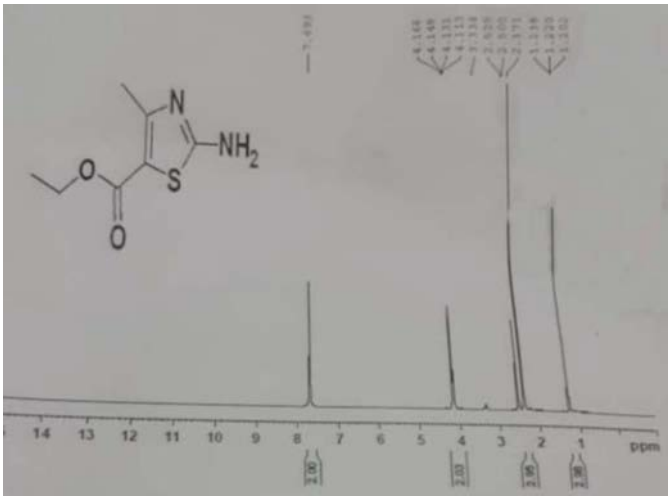
Preparation of Thiazole

To a mixture of ethyl acetoacetate in water (50.0 ml) and tetra hydro lurane add NBS (0.06mol). The reaction mixture was stirred at room temperature for 2 hours and Thiourea 10 gm was added and the reaction mixture was heated to 80 ºC for 2 hrs after cooling to room temperature the reaction mixture was filtered to get rid of the insoluble substances, then NH3H2O was added to the filtrate. The resulting yellow floccules were stirred at room temperature for 10 minutes and filtered. The filtrate cake was washed with water and recrystallized with ethyl acetate, then dried to get the target compound.

Yield: 95% (M + H+) = 186

Melting point = 312 ºC

Isolated compound submitted to 1HNMR



1H NMR (DMSO): δ 10.3(1H), δ 8.98(1H), δ 8.27(1H), δ 8.00(1H) and δ 7.76(1H)

Preparation of Quinoline Thiazole compound

A mixture of aldehyde and Thiazole was refluxed in methanol (30ml) on a water bath for 6 hrs. The reaction contents were cooled to room temperature and workup done with water. The resulting solid was filtered, washed with sodium sulphate solution and then with water, dried and recrystallized from ethanol to give the target compound

Chemical Formula: C16H13ClN4O2S

Yield = 25%

Melting Point

Isolated compound submitted to Spectral analysis

IR

The peaks obtained in the IR spectrum of Quinoline-Thiazole are significantly supporting the structure proposed for the Ethyl 2-Chloroquinoline-3-yl) Methylene amino)-4-methylthiazole-5-carboxylate.

Peaks may be assigned as follows

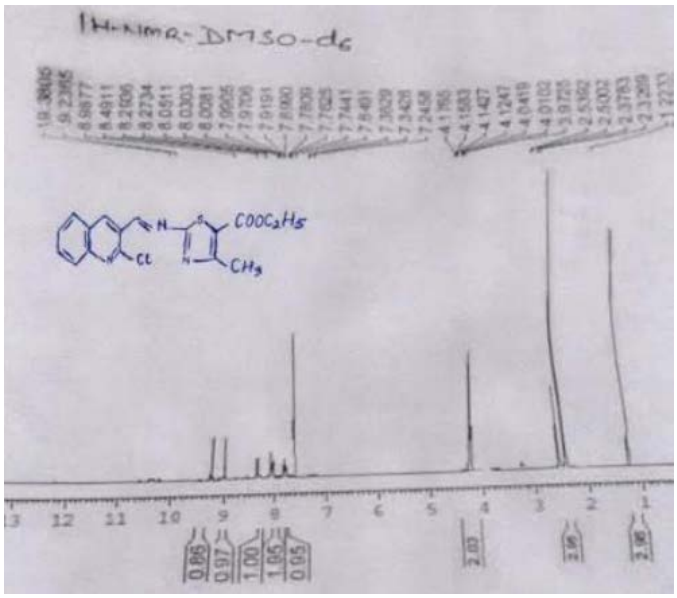
Sr. No.	Frequency cm-1	Assignment
1.	3388	-N-H stretch
2.	2939	-C-H stretch
3.	1760	C=O stretch
4.	1621,1532	NH bending
5.	1032	C-N stretch

Mass

The mass spectrum of isolated Quinoline-Thiazole compound showed molecular ion peak at 361 in positive mode implying the molecular weight of 360.82.

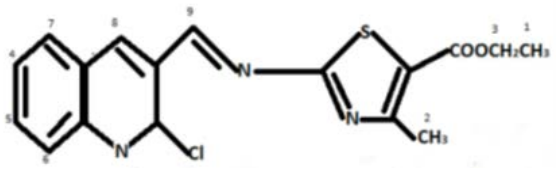
NMR

The 1H NMR spectrum of Quinoline-Thiazole compound was recorded by using DMSO as solvent.



The peaks obtained in the NMR spectrum of Ethyl 2-Chloroquinoline-3-yl) methylene amino)-4-methylthiazole-5-carboxylate are significantly supporting the proposed structure of the Ethyl 2-Chloroquinoline-3-yl) methylene amino)-4-methylthiazole-5-carboxylate.

Peaks obtained in the NMR spectrum may be assigned as follows



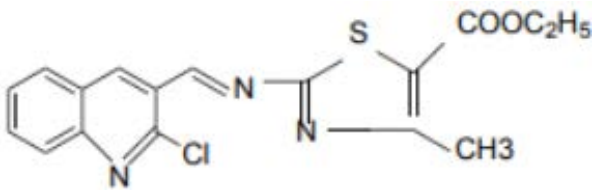
Sr. No.	δ(ppm)	Relative protons	Proton Assignment
1.	9.9	1	9
2.	8.98	1	8
3.	8.27	1	7
4.	7.97	2	5.6
5.	7.34	1	4
6.	4.11	2	3
7.	2.52	3	2
8.	1.22	3	1

On the basis of above spectral studies the structure of the synthesized Quinoline-Thiazole compound has been depicted.

Conclusion

Quinoline-Thiazole compound have been prepared by the reactions of different chemical compounds. First aniline reacts with acetyl chloride to give acetanilide. Acetanilide undergoes Vilsmeier reaction by involving use of DMF and POCl3 to give aldehyde. Ethyl acetoacetate on the other hand reacts with THF and Thiourea to yield Thiazole. Aldehyde then reacts with the Thiazole in presence of glacial acetic acid to give the desired compound.

The structure of the final compound was studied by spectral analysis and the proposed structure of the compound is depicted as follows.



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