RESEARCH ARTICLE

# SYNTHESIS AND CHARECTERIZATION OF NEW SUBSTITUTED 4-IODOQUINOLINES

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ABSTRACT:

A facile and highly efficient method for the synthesis of 4-Iodo quinolines in good to excellent yields by using inexpensive chemicals to reduce the cost. The present work describes the synthesis of highly substituted and noval 4-iodoquinolines involves the condensation of substituted anilines with ethyltrifluoroacetoacetate in presence of Copper Triflate which leads to the formation of substituted 4-hydroxyquinoline.

KEYWORDS: *Quinoline, Iodoquinolines, NMR Spectroscopy.*

## Introduction:

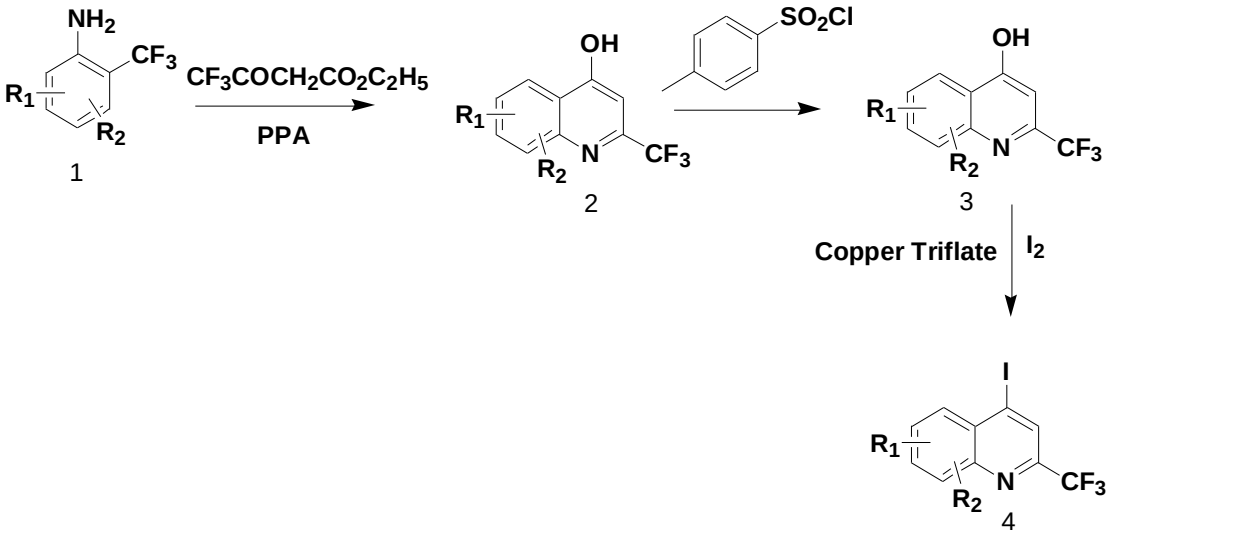
Most of the antimalarial agents contain quinoline ring as a core structure. Particularly, 4-haloquinolines are the key intermediates to build up further molecule. There are various methods for the preparation of 4-iodoquinolines. Arylthallium di-fluoroacetate on decomposition with aqueous potassium iodide gives aryl iodide.[1] Chloroquinoline on halogen exchange reaction with sodium iodide in acetonitrile at 120$^{o}$C for 24 hrs gives 4-iodoquinoline[2]. 4-Chloroquinoline on reaction with hydroiodic acid (47%)at 130$^{o}$C for 5 hrs gives 4-iodoquinoline [3].

Recently, a practical method has been reported [4]for the synthesis of 2,8-bis (trifluoromethyl)-4-hydroxyquinoline. Due to importance of 4-iodoquinoline in pharmaceuticals, we have planned to synthesise the substituted 4-iodoquinoline using inexpensive and easily available chemicals.

The main objective of the research was to prepare haloquinolines using non-hazardous chemicals, to device general procedure for the preparation of substituted 4-haloquinolines and to perform reaction at low temperature by using inexpensive chemicals to reduce the cost.

The present work describes the synthesis of highly substituted and noval 4-iodoquinolines following earlier procedure.[4] It involves the condensation of substituted anilines with ethyltrifluoroacetoacetate in presence of Copper Triflate which leads to the formation of substituted 4-hydroxyquinoline. The better leaving group O-tosyl derivative was prepared by the reaction of hydroxyquinoline with paratoluene sulphonyl chloride by neutralizing with aqueous sodium hydroxide. Further, tosyloxy derivative was converted into 4–Iodo by the action of Copper Triflate, iodine in glacial acetic acid.

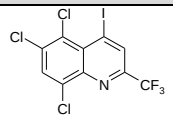
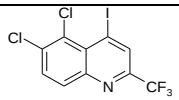
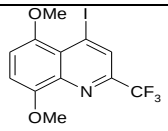
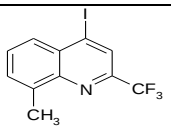
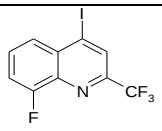
Reaction Scheme:

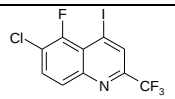
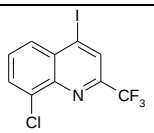
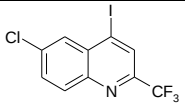
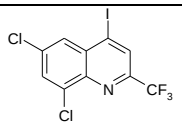
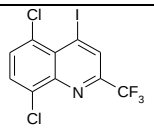
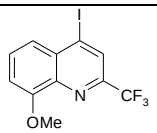



**R1, R2 = Alkyl, Alkoxy, Choro, Fluoro**

RESULTS & DISCUSSION:

Melting point were recorded on Buchi R-535 apparatus and are uncorrected. IR spectra were recorded on a Perkin – Elmer FT-IR 240- C spectrophotometer using KBr optics. Column chromatography was performed using hexane or a mixture of hexane and ethyl acetate.

| S.No | Product 4(a-k) | MP | Color | Yield |
|---|---|---|---|---|
| 4A |  | 98 °c | White | 80 |
| 4B |  | 118 °c | pale yellow | 82 |
| 4C |  | 115 °c | dark yellow | 78 |
| 4D |  | 285 °c | white solid | 84 |
| 4E |  | 62 °c | white solid | 80 |

| | | | | |
|---|---|---|---|---|
| 4F |  | 104 °c | white solid | 78 |
| 4G |  | 80 °c | white solid | 82 |
| 4H |  | 186°c | white solid | 80 |
| 4I |  | 194 °c | white solid | 78 |
| 4J |  | 96 °c | white solid | 84 |
| 4K |  | 112 °c | white solid | 84 |

**EXPERIMENTAL SECTION:**

**2–Trifluoromethyl–-5,8–Dimethoxy–4-Hydroxyquinoline (2):**

In a 250 ml two necked round bottom flask fitted with dropping funnel Polyphosphoric acid was taken and heated up to 90 °C. Then ester was added in a span of 30 min dropwise with the help of dropping funnel and allowed to stir for some time. Then temperature was raised to 100 °c and 2,5 Dimethoxy aniline was added carefully in a span of 2 hrs. Foaming was observed during addition which indicates that the reaction was going on. After addition, the reaction mixture was heated for 2 hrs at the temperature of 125 °C and left for overnight.

The reaction mixture was poured in ice cold water with stirring and stirring continued for 2 hrs. Separated crystalline solid filtered, washed with water and dried. The structure and purity of the compound has been established with the help of physical and spectral data and TLC.

**2–Trifluoromethyl–5,8-Dimethoxy-4-Tosyloxyquinoline(3) :**

In a round bottom flask, 2–Trifluoromethyl–5,8-Dimethoxy – 4-hydroxyquinoline was dissolved in 30 ml acetone. To this mixture, acetonyl solution of p-toluene sulfonyl chloride was added and the mixture was cooled in ice cold water bath. Then sodium hydroxide solution was added drop wise with stirring till neutral pH (~ 7.5). It was stirred for additional 1 hr in cold condition. Separated solid was filtered, washed with water and hexane.

**GENERAL PROCEDURE:**

**2 –Trifluoromethyl—5,8-Dimethoxy-4–Iodoquinoline (A-K)**

A cold mixture of Copper Triflate and Red Phosphrous was taken in a 250 ml two necked round bottom flask. It was stirred for 30 min and cooled to 10 °C. Iodine was added to this stirring reaction mixture in a span of 1.5 hrs. After that it was stirred for additional 3 hrs at the same temperature. Then 2-Trifluoromethyl—5,8-Dimethoxy-4–

Tosyloxyquinoline was added portion wise in a span of 0.5 hr . The whole reaction mixture was stirred for 3 hrs in cold condition and then left overnight at room temperature. The reaction mixture was diluted with 50 ml of chloroform and 50 ml of water. It was stirred well and the chloroform layer was separated out with the help of separating funnel.

Then it was washed with 30 ml of 10% sodium bicarbonate and 30 ml of 10% sodium meta bisulphate solutions and dried over sodiumsulphate. The chloroform layer was concentrated and the residue was purified through column using hexane. Following the same procedure other derivatives (4A-K) have been prepared and Characterized by M.P. I.R , NMR, Mass spectral data.

**4A).5, 6, 8-Trichloro-4-Iodo-2-Trifluoromethyl-Quinoline.**

Mass : 422

IR (KBr, $cm^{-1}$) : 1135, 1333(C–F), 1536(C–C), 1468(C=C), 1581(C=N), 791(C–Cl)

$^1H$ NMR (300 MHz, CDCl3) : 8.1(s, 1H), 8.65 (s, 1H).

**4C).4-Iodo-5, 8-Dimethoxy-2-Trifluoromethyl-Quinoline**

Mass : 380

IR (KBr, $cm^{-1}$) : 1131, 1328(C–F), 1437(C=C), 1477(C–C), 158(C=N), 1110(C–O–C)

$^1H$ NMR (300 MHz, $CDCl_3$) : 8.4(s, 1H), 6.95(d, *J*=9.065, 1H), 7.0(d, *J*=9.065, 1H), 4.05(s, 3H), 3.95 (s, 3H)

**4E).8-Fluoro-4-Iodo-2-Trifluoromethyl-Quinoline.**

Mass : 342

IR(KBr, $cm^{-1}$) : 1145, 1329(C–F), 1475(C=C), 1489(C–C), 1567(C=N).

$^1H$ NMR (300, $CDCl_3$): 8.3(s, 1H), 7.9(d, J=8.498, 1H), 7.7(m, 1H), 7.55(t, 1H)

**4H).6-Chloro-4-Iodo-2-Trifluoromethyl-Quinoline.**

Mass : 358

IR (KBr, $cm^{-1}$) : 1146, 1333(C–F), 1447(C=C), 1479(C–C), 1570(C=N), 812(C-Cl).

$^1H$ NMR (300, $CDCl_3$): 8.38(s, 1H), 8.2(m, 2H), 7.8(d, J=9.065, 1H).

**4K). 4-Iodo-8-Methoxy-2-Trifluoromethyl-Quinoline.**

Mass : 350

IR (KBr, $cm^{-1}$) : 1125, 1331(C–F), 1438(C=C), 1497(C–C), 1559(C=N), 1006(C-O-C).

$^1$ H NMR (300, $CDCl_3$): 8.3(s, 1H), 7.65(d, *J*=8.081, 2H), 7.15(t, J=9.442, 1H), 4.1(s, 3H).

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