Synthesis of Various Ethyl 2-(Ethoxyphosphono)-1-Cyano-2-(Substituted Tetrazolo[1,5-A]Quinolin-4-yl)Ethanoate Derivatives using Alumina (Basic)

A PG Dissertation Report of a Project Carried out as a Part of Curriculum for the Degree of Master of Science in Organic Chemistry

SUBJECT CODE: 33424C
[CBOP-5 CHO-453 C]

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SAVITRIBAI PHULE PUNE UNIVERSITY, PUNE

(2020-2021)

DECLARATION BY THE STUDENT

I declare that the dissertation entitled **"Synthesis of Various Ethyl 2-(Ethoxyphosphono)-1-Cyano-2-(Substituted Tetrazolo[1,5-A]Quinolin-4-yl)Ethanoate Derivatives using Alumina (Basic)"** submitted by me for the degree of Master of Science in Organic Chemistry **SUBJECT CODE: 33424C [CBOP-5 CHO-453 C]** is the record of work carried out by me under the guidance of **DR. AMOL H. KATEGAONKAR** and has not formed the basis for the award of any degree, diploma, associateship, fellowship, titles in this or any other University or other institution of Higher learning. I further declare that the material obtained from other sources has been duly acknowledged in the dissertation

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CERTIFICATE OF RESEARCH SUPERVISOR (GUIDE)

Certificate of the Guide CERTIFIED that the work incorporated in the PG dissertation entitled **"Synthesis of Various Ethyl 2-(Ethoxyphosphono)-1-Cyano-2-(SubstitutedTetrazolo[1,5-A]Quinolin-4-yl)Ethanoate Derivatives using Alumina (Basic)"** submitted by **MR. MAHESH RAJARAM MHASKE** was carried out by the candidate under my supervision/guidance. Such material has been obtained from other sources has been duly acknowledged in the dissertation.

Date: -
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EXAMINERS' CERTIFICATE

This is to certify that PG dissertation entitled "**Synthesis of Various Ethyl 2-(Ethoxyphosphono)-1-Cyano-2-(Substituted Tetrazolo[1,5-A]Quinolin-4-yl)Ethanoate Derivatives using Alumina (Basic)**" submitted by **MR. MAHESH RAJARAM MHASKE** was carried out by the candidate under supervise of **DR. AMOL H. KATEGAONKAR.**

With this understanding, we consider the fact that the PG dissertation is a well written project report, should be appreciable and the project work carried out is commendable, we recommend that the PG dissertation submitted by **MR. MAHESH RAJARAM MHASKE** be accepted in its present form for the award of Master of Science in Organic Chemistry, Savitribai Phule Pune University, Pune. He is successfully defended the Viva-Voce Examination.

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ACKNOWLEDGEMENT

I would like to take the privilege to thank the selfless people from the core of me heart who with their constant support, affection, inspiration and encouragement made us feel comfortable to successfully complete this venture.

My deep sense of gratitude and harmful thank to my PG Dissertation Project Guide/Supervisor **Dr. Amol H**. **Kategaonkar** for his expert guidance, constant encouragement, stimulating discussion.

I am thankful **to Dr. (Mrs.) J. D. Sonkhaskar** Principal, MVP Samaj's KSKW ASC College, CIDCO, Uttamnagar, Nashik and **Dr. S. K. Kushare** Head Department of Chemistry, for support and providing all the necessary facilities during the course of my project work and guided me in light path of the life.

It is my privilege to express our gratitude and sincere thanks to my family for their unconditional love prayer and moral support.

My acknowledgement is many more what I have expressed here.

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SYNTHESIS OF VARIUOS ETHYL 2-(ETHOXYPHOSPHONO)-1-CYANO-2-(SUBSTITUTED TETRAZOLO[1,5-A]QUINOLIN-4-YL)ETHANOATE DERIVATIVES USING ALUMINA (BASIC).

INDEX

1. GENERAL INTRODUCTION

The Knoevenagel condensation is a powerful, general, and frequently used reaction for the formation of carbon–carbon bonds[1] The product obtain is α,β-unsaturated compound which is mostly used as intermediate in the formation of natural products[2] In this reaction, nucleophilic addition takes place to a carbonyl compound by an active methylene compound, which is accompanied by dehydration. It often results in an α,β-conjugated enone or electrophilic alkene .The electrophilic alkenes are versatile intermediates in organic synthesis and have widespread applications for the synthesis of various important organic compounds, viz polymers, natural products, fine chemicals, fluorescent dyes.[3] Many organic condensation reactions such as the Henry and Claisen Schmidt reactions also occur in the similar fashion as the Knoevenagel reaction involving different types of nucleophiles. Therapeutic agents, adequate chemicals[4,] polymers having different functional groups[5], insecticides and pesticides. It is usually carried out in organic solvents and catalyzed by organic bases such as pyridine or piperidine[6]

In modern-day synthetic organic chemistry, the carbon– carbon bond formation is a crucial reaction for producing various α,β-unsaturated acids. These acids are widely used as intermediates for the synthesis of pharmaceuticals, polymers, and cosmetic product[7]. Emil Knoevenagel is generally regarded as a pioneer in the field of the carbon–carbon bond formation with his discovery in 1894 of the reaction of formaldehyde with diethyl malonate. In the presence of diethylamine as a catalyst, Emil Knoevenagel demonstrated that a bis adduct product was formed[8]. Two years later, in 1896, Knoevenagel verified that with the addition of piperidine as a catalyst, a similar carbon–carbon bond formation reaction was possible using aromatic aldehyde compounds[9]. Piperidine is often regarded as the cyclic form of diethylamine. In modern-day chemistry, some aromatic aldehyde compounds are of particular interest from a biobased perspective. Several aromatic aldehydes are likely to be derived from lignin. Lignin is a naturally occurring biopolymer available at a large-scale from the waste products generated by the paper industry[10]. Extending these aromatic aldehyde compounds in a "Knoevenagel-likeway" could provide many precursors and intermediate compounds for the pharmaceutical industry in a biobased manner[11].

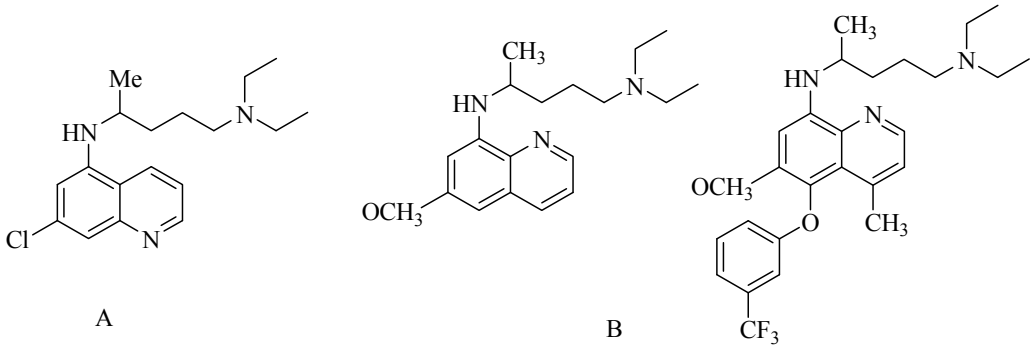
Generally, organocatalysis uses small organic molecules instead of toxic transition metal compounds. Organic molecules are commonly insensitive to oxygen and moisture in the atmosphere, so there is no need for exclusive reaction vessels or extreme-dry reagents and solvents[12]

A] IMPORTANCE OF QUINOLINE

In last few years five & six membered heterocyclic compounds containing one or two heteroatom fused to quinoline ring gains importance in natural products as well as in the synthetic compounds of biological interest [13].

Quinoline derivation having potent, pharmacological applications due to their significant antimalarial[14], anti-inflammatory, antitumore[15,16], antibacterial & antiviral activities[17].

The best compound that emerged from this endeavor is chloroquine[18], During the past six decades CQ have been the frontline antimalarial agents (A) because of their therapeutic efficacy & lower cost. Primaquine (B) have been applied as a chemotherapeutics for the treatment of malaria disease.



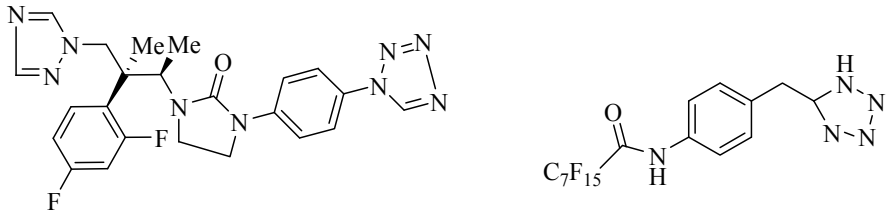
Chloroquine (A) and Premaquine (B, both)

B] IMPORTANCE OF TETRAZOLO

The outstanding achievements of the pharmaceutical chemistry in the last detail are due in no small way to the creation of novel drugs containing a tetrazolo ring as structural fragment. Tetrazole compound have a wide range of pharmaceutical applications[19]. These compounds have anti-inflammatory, antilipemic, antimicrobial &antiallergic activities[20].

Momose et al [21] Studied series of perfluoroamides that may prove useful for the treatment of diabetes & contain a tetrazole ring as the acidic fragment have been studied actively in recent years.

Unlike fungicidal preparations of the first- and second-generation azole type the tetrazole containing preparations exhibit high activity against Candida, Cryptococcus, and Aspergillus with peroral administration. A water-soluble form TAK-457 for injections was developed on the basis of TAK-456.

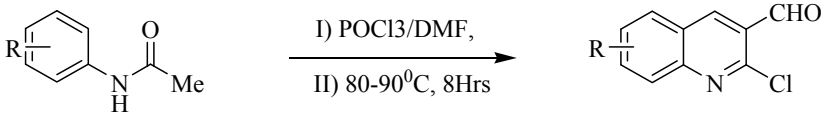


TAK-456 Perfluoroamides

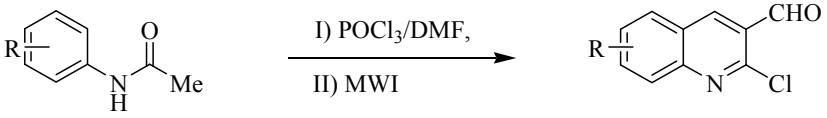
2. LITERATURE SURVEY:

A] 2-chloro-3-formyl quinoline

i) Raghunathan R et.al, synthesized 2-chloroquinoline-3-carbalehydes from acetanilides via a Vilsmaier Haack reaction[22].

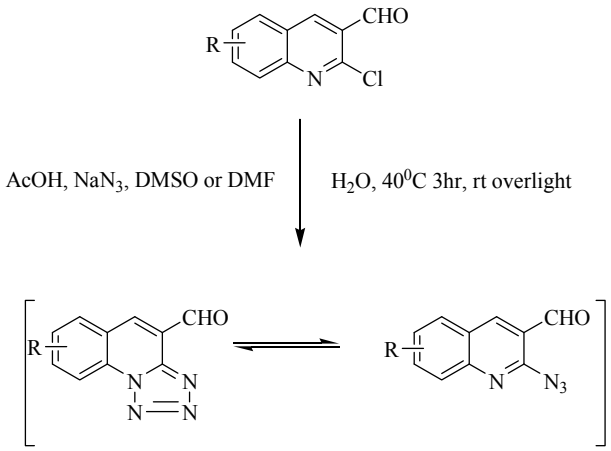


ii) Rao. R. B. et.al. synthesized 2-chloroquinoline -3-carbaldehyde from acetanilides via a Vilsmair Haack reaction by microwave irradiation[23].

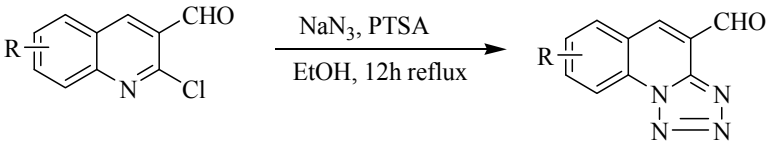


B] Tetrazolo[1,5-1] Quinoline-4-carboaldehyde.

i) R. E. kamel et.al. synthesized 2-azidoquinoline-3-carbaldehydes from reaction of 2chloroquinoline 3- carbaldehyde with sodium azide in DMSO or DMF and their ring – chain tautomerism discussed[24].

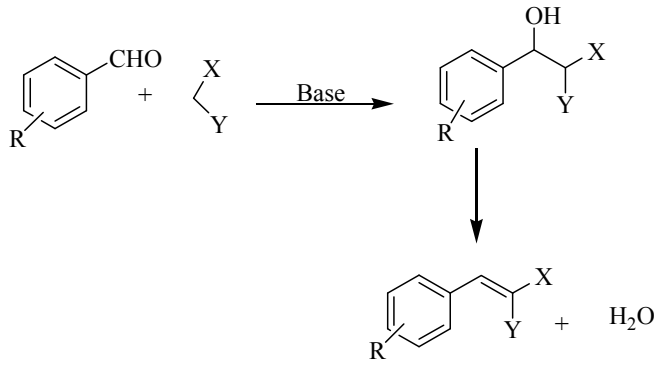


ii) S. K. Gupta et.al. synthesizedtetrazolo [1,5-1] quinolone -4-carboaldehyde from reaction of 2chloro -3- formyl quinolone with NaN_3 and PTSA in ethanol[25].



C] Knoevenagel condensation reaction:

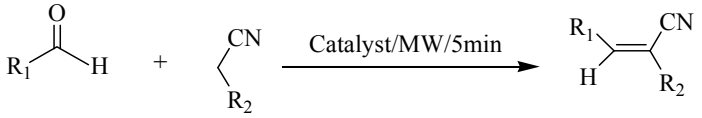
1] The Knoevenagel condensation is an important C-C bond forming reaction which has been extensively studied and also applied in industrial processes. Although it involves a dehydration step, the reaction can be successfully carried out in water to produce electron deficient alkenes and heterocyclic compounds such as coumarins[26].



Scheme 1

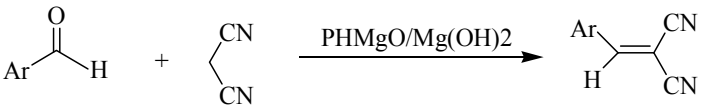
X,Y=EWG

2] A sustainable Knoevenagel condensation of a series of aldehydes with malononitrile and ethyl cyanoacetate is described. The process is based on the combination of microwave activation and hydroxyapatite catalysis under solvent-free conditions. Products are obtained in and high yields after short reaction times[27].



Scheme 2

3] Herein, an operationally facile and efficient Knoevenagel reaction catalyzed by porous hierarchical MgO/Mg(OH)2 . Condensation of various aldehydes malononitrile proceeds under mild conditions and gives the target products with high yields[28].



Scheme 3

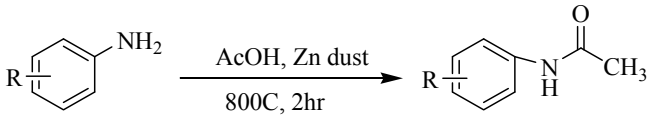
3.1 SECTION A: SYNTHESIS OF 2-CHLORO, 3-FORMYL QUINOLONES & DERIVATIVES

Section A*: Synthesis of 2-chloro, 3-formyl quinolones & derivatives*.

Various substituted acetanilides 2(a-d) were synthesized using different aromatic anilines 1(a-d). For synthesis of acetanilide acetic acid/Zn dust at 80 ^{0}C was used which was further required to synthesized substituted formyl quinolines.

2-chloro-3-formyl quinolone derivatives were synthesized from different acetanilides which were prepared from different substituted aromatic anilines. The Vilsmair-Haack reagent has been proved to be a versatile reagent capable of executing a large variety of synthetic transformation.

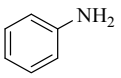
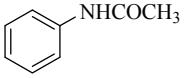
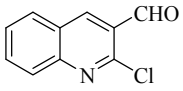
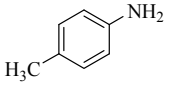
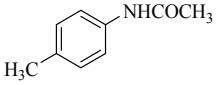
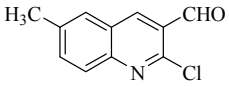
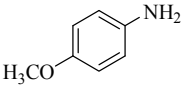
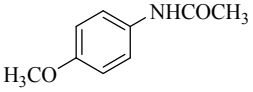
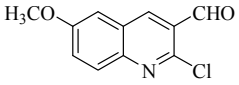
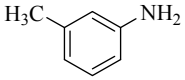
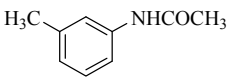
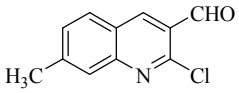
Scheme – 1 :Synthesis of Substituted 2-chloro-3-formyl quinoline.



3.1.1 RESULTS AND DISCUSSIONS

In the first step diff. substituted anilines 1(a – d) were used to prepare substituted anilines 1(a-d) were used to prepare substituted acetanilides 2(a-d) In second step prepared substituted acetanilides were used to synthesis 2-chloro-3-formyl quinoline [3 a-d] Different electron donating & withdrawing groups were used to check the versatile nature of synthesis. The Vilsmeier cyclization of acetanilides was carried at 0-5^{o}C by using $POCl_3$ & DMF followed by heating at 80-90^0 C to afford 2-chloro-3-formyl quinoline 3(C1-C4)

Table*: Synthesis of Substituted 2-chloro-3-formyl quinoline*

Comp	Anilines (1)	Acetanilide (2)	Quinolines (3)	% Yield*	M.P. (^{0}C)
C1				80	148-150
C2				77	124- 126
C3				71	146-148
C4				74	136-138

*Yields were isolated

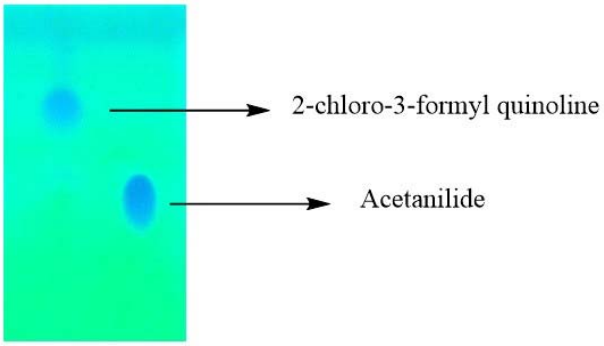
3.1.2 EXPERIMENTAL PART

General procedure for Synthesis of 2-chloro-3-formyl quinoline 3(C1-C4):

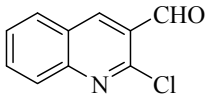
Dimethyl formamide [DMF]5ml was taken and is cooled to 0-5^{0}Ctemperature in a flask then to it 18ml of $POCl_3$ is added drop wise with constant stirring. Then to this solution 4 gm of acetanilide was added by maintaining the temperature. After few minutes stirring the solution of reaction mixture was reflux for 8 to 10 hr. 80-90^{0}C.

Completion of reaction was confirmed by TLC. After completion of reaction, there action mixture was cooled and poured in 100ml beaker containing crushed ice and stirred about half an hour. Then Precipitate was obtained was filter and the residue was washed with cold water and dried. The obtained product was recrystalysed from ethyl acetate. Yields were isolated and Melting point of the product was carried out. Further confirmation of product was done by spectral analysis.

TLC Plate of confirmation of *2-chloro-3-formyl quinoline* preparation.



3.1.3 SPECTRAL ANALYSIS:



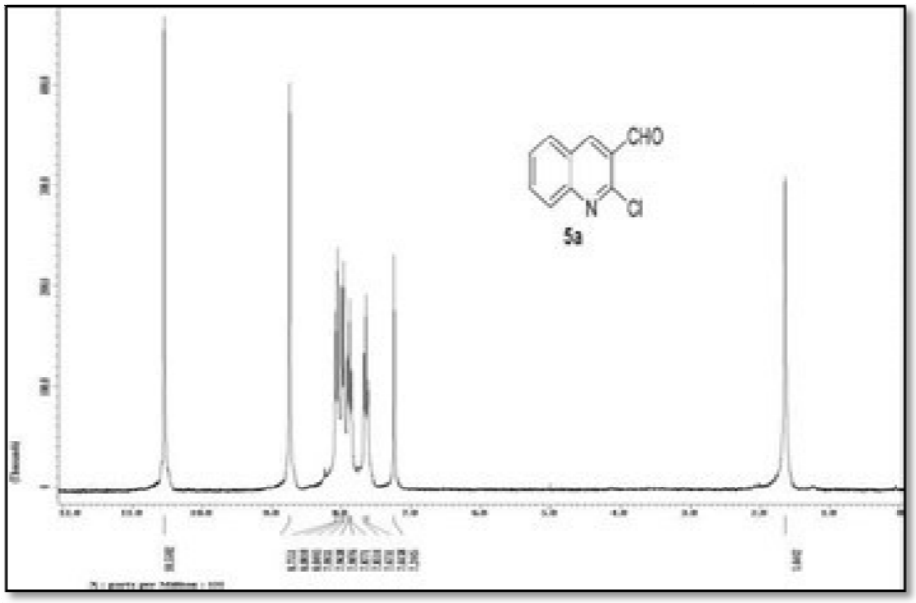
2-chloroquinoline-3-carbaldehyde (C1): Recrystallization Solvent: Ethyl acetate; yellow pale solid, mp 145-146 ^{0}C.

IR (KBr): 3043 (st. C-H), 2872 (st. C-H), 1688 (st. C=O), 1615-1553 (st. C=C) cm^{-1} .[1]

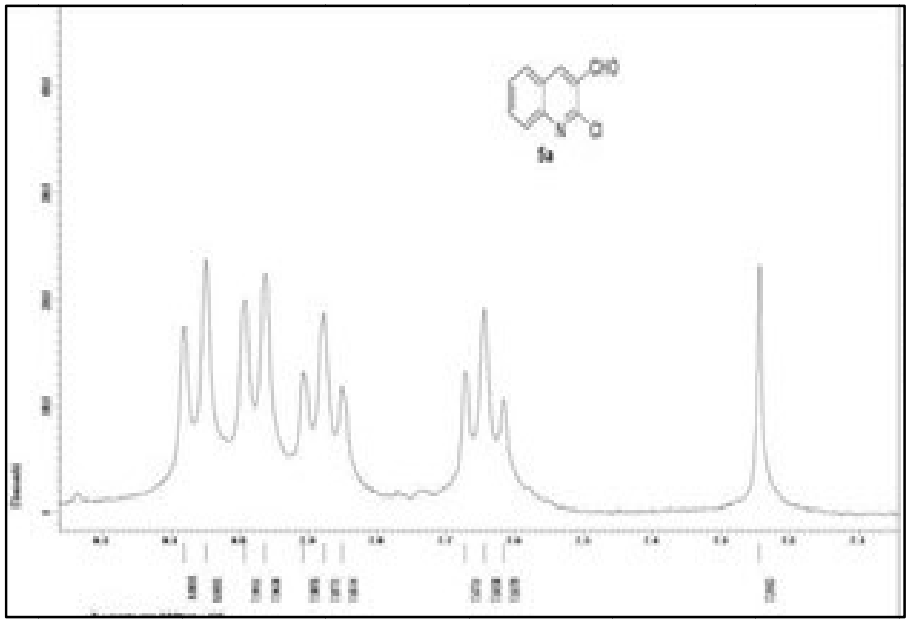
^{1}H NMR (270 MHz, *J* Hz, $CDCl_3$) δ: 10,55 (s, 1H); 8,76 (s, 1H); 8,07 (d, *J*=8,6; 1H); 7,98 (d, *J*=7,9; 1H); 7,89 (dd, *J1*=8,3; *J2*=7,7; 1H); 7,64 (dd, *J1*=8,3; *J2*= 7,9; 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 189,4 (d); 150,3 (s); 140,5 (d); 133,7 (d); 130,6 (s); 129,6 (s); 129,1 (d); 127,7(d); 126,6 (d); 121,2.

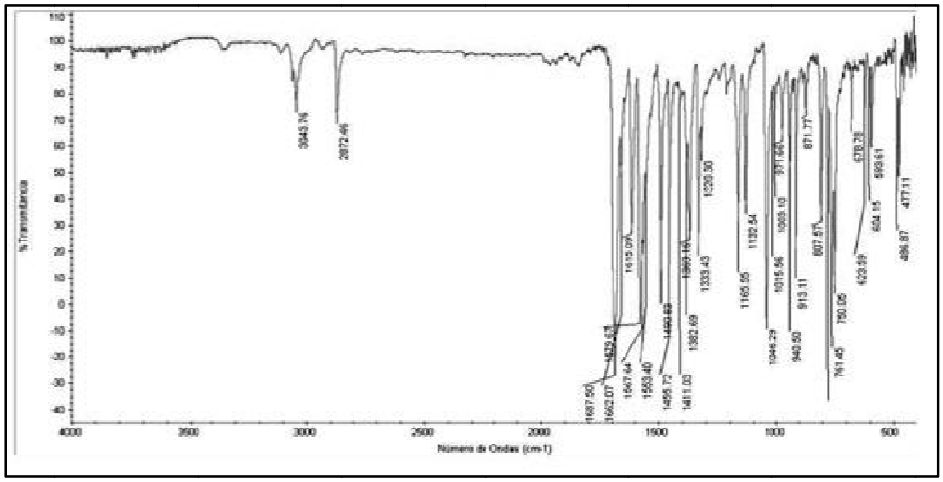
^{1}H NMR Spectra



^{13}C NMR Spectra



IR Spectra

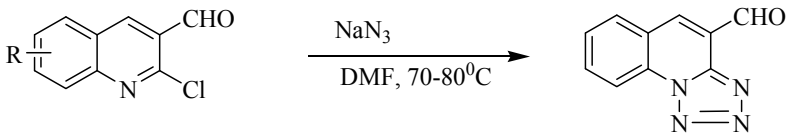

% Transmittance
Numero de Ondas (cm-1)
4000
3500
3000
2500
2000
1500
1000
500
3843.76
2872.46
1615.07
1647.64
1553.40
1455.72
1411.03
1382.69
1339.43
1259.50
1165.05
1132.54
1069.10
1015.56
971.66
940.50
913.11
871.77
807.67
761.45
750.05
678.28
654.15
620.59
599.61
486.87
477.11

3.2 SECTION B: SYNTHESIS OF TETRAZOLO [1,5-A]QUNOLINE-4-CARBALDEHYDE DERIVATIVES

Section B: *Synthesis of tetrazolo [1,5-a]qunoline-4-carbaldehyde derivatives*.

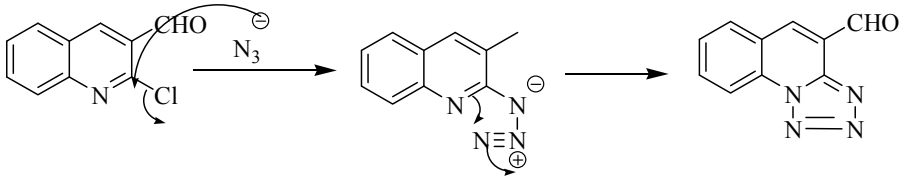
In the present work we have synthesized tetrazolo [1,4-a] quinoline-4-carbaldehyde derivatives from substituted 2-chloro-3-formyl quinolines by adding sodium azide in DMF at 70-80 ^{0}C.

Reaction:



Scheme : 2 Synthesis of tetrazolo[1,5-a]quinoline-4-carbalidehyde derivatives

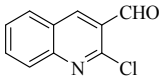
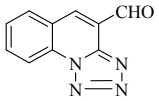
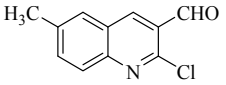
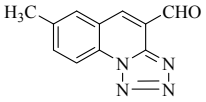
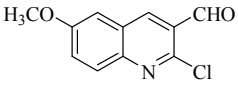
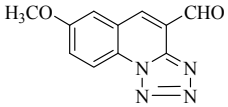
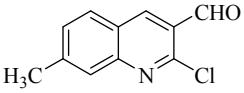
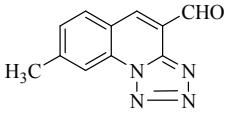
Mechanism:



3.2.1 RESULTS & DISCUSSIONS.

Different substituted 2-chloro-3-formyl quinolones were examined for the synthesis of tetrazolo[1,5-a]quinolines which afford good yield. Reaction proceeds smoothly in DMF at 60 – 70^0 C and all the isolated compounds gives good to excellent yields through simple work up procedure. Effect of electron donating makes the product yield increased instead of electron withdrawing. The result of product yield obtained and melting points where recorded was mention in Table 2.

Table2 :*Synthesis of tetrazolo [1,5-a] Substituted Qunoline -4-carboaldehyde derivative*

Comp	Reactant	Product(D1-D4)	Time(hrs)	*Yield(%)	M.P (^{0}C)
D1			7	89	139-141
D2			7	90	188-190
D3			7	88	98-100
D4			7	84	178-180

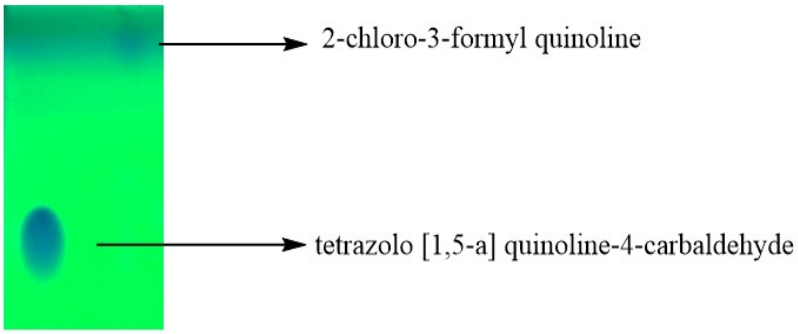
*Yields were isolated.

3.2.2 EXPERIMENTAL PART

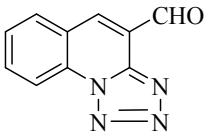
General procedure: *Synthesis of tetrazolo [1,5-a] quinoline-4-carbaldehyde derivative.*

2 gm of substituted 2-chloro-3-formyl quinoline and 1.2 gm of sodium azide was added in DMF. There action mixture was stirred at 60 – 70^0 C of 7-8 hours. Completion of reaction was confirmed by TLC using Ethyl acetate: n-Hexane as mobile phase (ratio 6:4). After completion of reaction the reaction mixture was poured on ice cold water. The obtained product was filtered and dried. The melting point was carried out and compared with literature data. The obtained product was confirmed using spectral analysis.

TLC Plate

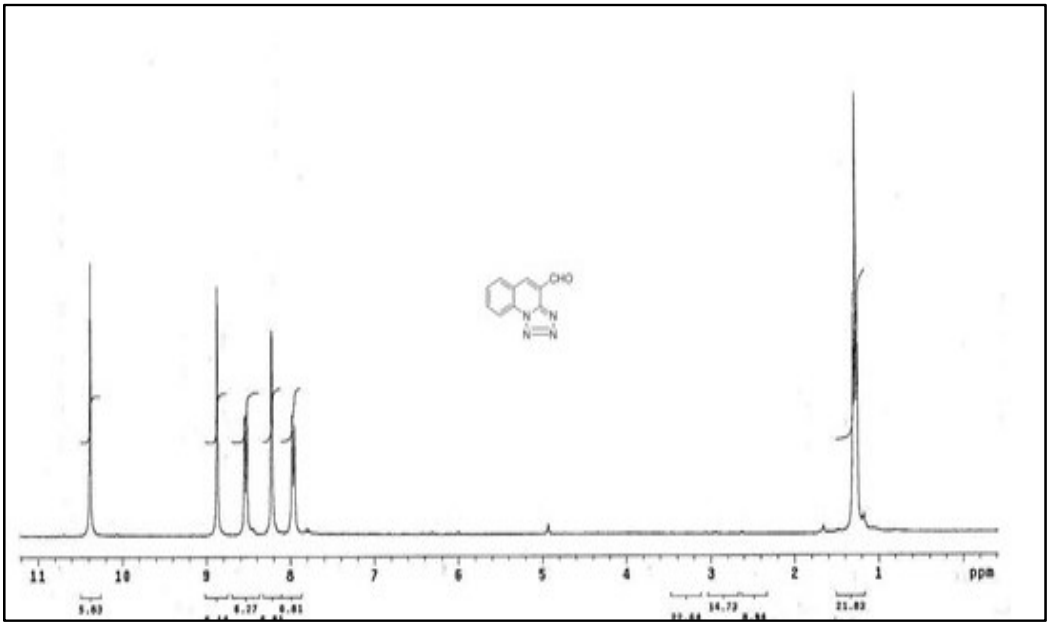


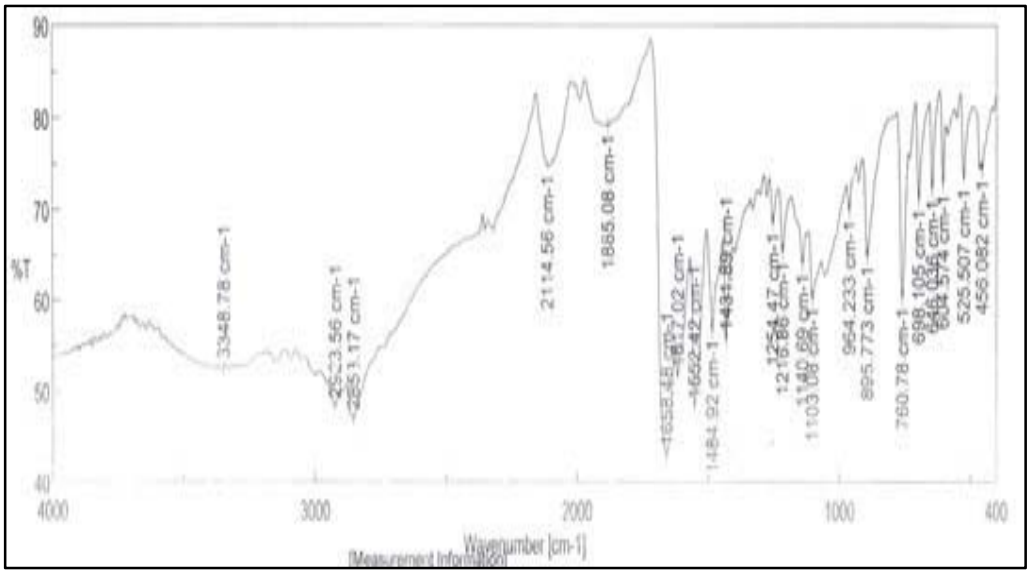
3.2.3 SPECTRAL ANALYSIS



IR: 2923 cm^{-1} (Ar-CHO Strec.), 3348 (tetrazole N≡N), 1885 (C=O).

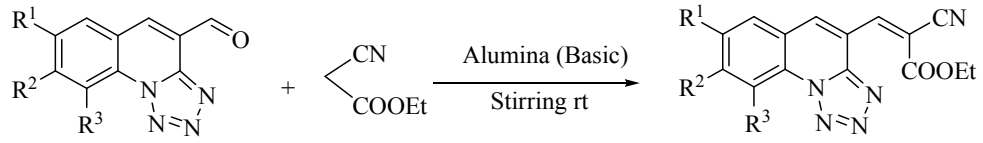
^{1}H NMR (DMSO-*d6*, 300 MHz): 7.96 (d, 1H, Ar-H), 8.22 (s, 1H, Ar-H), 8.53 (d, 1H, Ar-H), 8.87 (s, 1H, Ar-H), 10.38 (s, 1H, CHO).




90
80
70
60
50
40
%T
4000
3000
2000
1000
400
Wavenumber [cm-1]
3348.78 cm-1
2114.56 cm-1
1885.08 cm-1
1652.42 cm-1
1484.92 cm-1
1431.89 cm-1
1254.47 cm-1
1216.88 cm-1
1140.69 cm-1
1103.08 cm-1
964.233 cm-1
895.773 cm-1
760.78 cm-1
698.105 cm-1
604.574 cm-1
525.507 cm-1
456.082 cm-1

3.3 SECTION C: Synthesis Of Variuos Ethyl 2-(Ethoxyphosphono)-1-Cyano-2-(Substituted Tetrazolo[1,5-A]Quinolin-4-Yl)Ethanoate Derivatives Using Alumina (Basic) Via Knoevenagel Condensation

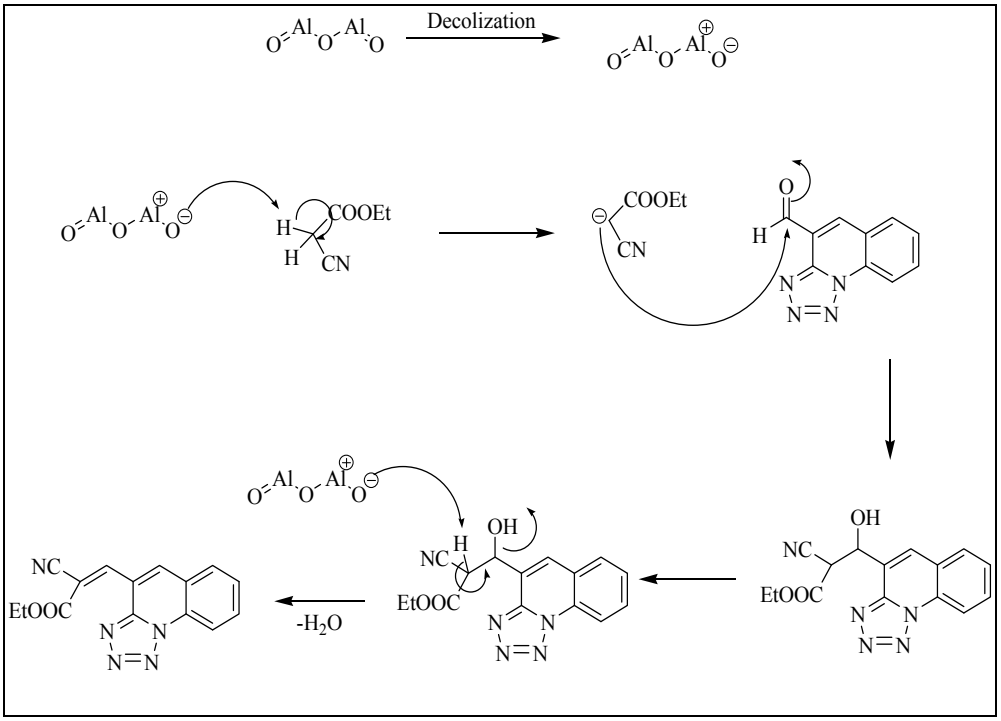
Reaction



(1a-i) **(2)** **(3a-i)**

We have synthesized ethyl 2-cyano-3-(tetrazolo [1,5-a]quinolin-4-yl)acrylate derivatives (3a-d) via Knoevenagel condensation reaction of ethyl cyano acetate (2) and tetrazolo[1,5-a]quinoline derivatives (1a-d) in the presence of Alumina (Al_2O_3) under room temperature condition in excellent yields.

Mechanism



3.3.1 RESULT & DISCUSSION

Reaction proceeds smoothly in Alumina at room temperature and all the isolated compounds gives good to excellent yields through simple work up procedure. Effect of electron donating makes the product yield increased instead of electron withdrawing. The result of product yield obtained and melting points where recorded was mention in Table1.

Table1:Synthesis of ethyl 2-cyano-3-(tetrazolo [1,5-a]quinolin-4-yl)acrylate derivatives (3a-d)

Compound	R_1	R_2	R_3	Yield[b] (%)	M. P. (^oC)
3a	H	H	H	86	166-168
3b	Me	H	H	79	192-194
3c	H	Me	H	88	202-204
3d	H	OMe	H	85	210-212

[a]*Reaction condition*: **6** (5 mmol), ethyl cyano acetate (5.2 mmol) and alumina (Basic) stirred at rt. [b]Isolated Yield

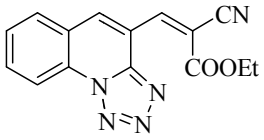
3.3.2 EXPERIMENTAL PART

General procedure for synthesis of ethyl 2-cyano-3-(substituted tetrazolo[1,5-a]quinolin-4yl)acrylates (3a-d)

To the stirred solution of tetrazolo[1,5-a]quinoline-4-carbaldehyde 1(5 mmol) and ethyl cyano acetate (5.2 mmol) and 3gmAlumina (Basic) at room temperature. The progress of the reaction was monitored on TLC. After completion of reaction, the reaction mixture was cooled to room temperature and poured on crushed ice. Recrystallization was done in ethyl acetate and the neutral alumina is recovered by simple filtration. The obtained crude product was purified by column chromatography on silica gel by hexane: ethyl acetate (8:2) as an eluent.

Infrared spectra were recorded on a matrix of potassium bromide with Perkin-Elmer 1430 spectrometer. ^{1}HNMR and ^{13}C NMR spectra were recorded on Varian NMR spectrometer, Model Mercury Plus(200MHz).

3.3.3 SPECTRAL ANALYSIS

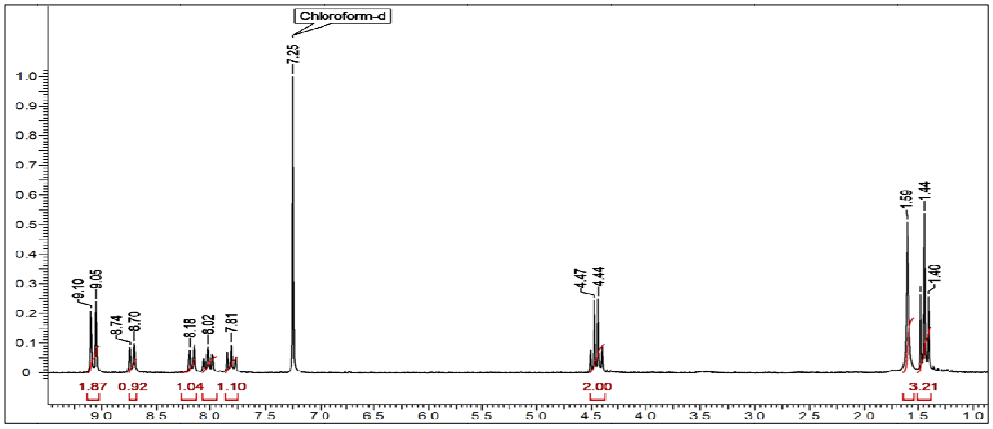


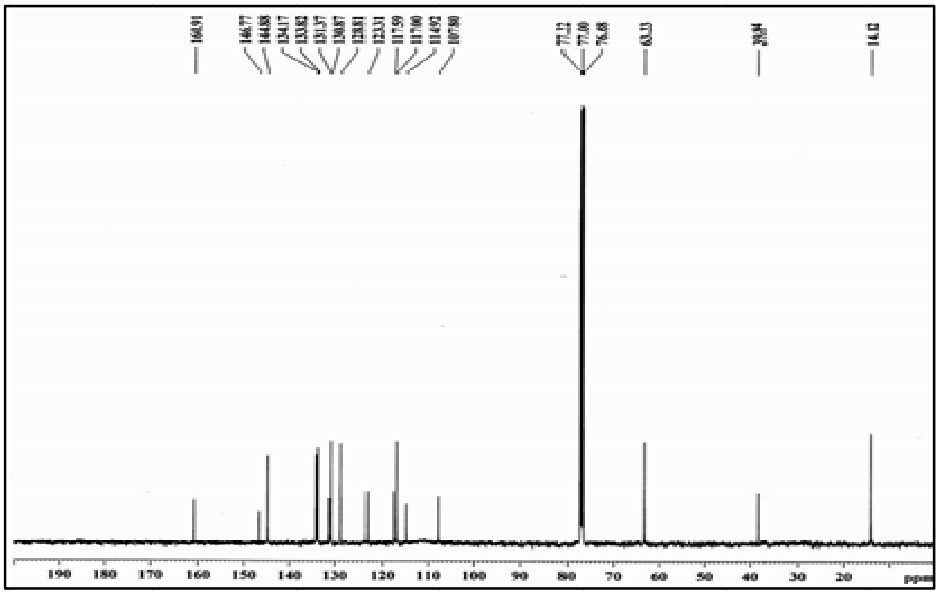
Ethyl 2-cyano-3-(tetrazolo[1,5-a]quinolin-4-yl)acrylate ***(3a)***

IR (KBr, υ_{max}/cm^{-1}): 2257 (C≡N), 1744 (COOEt), 1597 (C=N).

^{1}H NMR (200 MHz, $CDCl_3$, δ ppm): 1.44 (t, 3H, *J* = 7.2 Hz, O-CH_2-CH_3), 4.44 (q, 2H, *J* = 7.2 Hz, O-CH_2-CH_3), 7.81 (t, 1H, *J* = 6 Hz, Ar-H), 8.02 (t, 1H, *J* = 6 Hz, Ar-H), 8.18 (d, 1H, *J* = 8 Hz, Ar-H), 8.72 (d, 1H, *J* = 8 Hz, Ar-H), 9.05 (s, 1H, Ar-H), 9.10 (s, 1H, C=CH).

^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 14.12 (CH_3), 39.84 (OCH_2), 107.80 (CH-CN), 117.00 (CN), 117.59, 123.31, 128.81, 130.87, 131.37, 133.82, 134.17, 144.88, 146.77 (Ar-C), 157.2 (C=C), 160.90 (C=O).





4. CONCLUSIONS

We have synthesized ethyl 2-cyano-3-(tetrazolo [1,5-a]quinolin-4-yl)acrylate derivatives in excellent yields

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