SYNTHESIS OF SOME POTENT INTERMEDIATES FOR HETEROCYCLES

(Winter Research Program: Dec' 2016 –Jan'2017)

Submitted by,

Chayanika Dutta

B.Sc. 6th sem, Bahona College,

Jorhat; Assam

Carried out under the Supervision of

Dr. Pranjal Gogoi

Scientist, Applied Organic Chemistry Group

Chemical Science and Technology Division

CSIR-North East Institute of Science & Technology

Jorhat-785006, Assam

Roll No: 24420066

Declaration

I, Ms. Chayanika Dutta, winter trainee, Chemical Science and Technology Division, CSIR-North East Institute of Science and Technology, Jorhat-785006, Assam, declare that this report entitled **"SYNTHESIS OF SOME POTENT INTERMEDIATES FOR HETEROCYCLES"** is the result of my winter project. The duration of this project is Dec' 2016- Jan' 2017. I have carried out my project work under the guidance of **Dr. Pranjal Gogoi,** scientist, Applied Organic Chemistry Group, Chemical Science and Technology Division, CSIR-North East Institute of Science and Technology. I have fulfilled all the requirements for this winter project.

Chayanika Dutta

Chayanika Dutta.

CERTIFICATE

TO WHOM IT MAY CONCERN

It is to certify that Chayanika Dutta, a student of BAHONA COLLEGE, JORHAT of B.Sc. 6th semester has completed a project report on "SYNTHESIS OF SOME POTENT INTERMEDIATES FOR HETEROCYCLES" under my guidance and supervision. She has fulfilled the requirement laid down in the project report.

(**Dr. Pranjal Gogoi**)

Scientist, Applied Organic Chemistry Group
Chemical Science and Technology Division
CSIR-NEIST, JORHAT

ACKNOWLEDGEMENT

The preparation and completion of this report is not an individual effort. This gives me immense pleasure to express my sense of gratitude to **Dr. Pranjal Gogoi**, outstanding scientist, Applied organic Chemistry Division, CSIR-NEIST for his individual guidance, suggestions and encouragement throughout my whole project. I express my deepest sense of gratitude for giving me his valuable time and support.

I express my gratefulness to Dr. D. Ramaiah, Director, CSIR-NEIST, Jorhat, for allowing me and providing with the laboratory facilities to carry out my winter project work.

I also acknowledge the help and support rendered by head of the Applied Organic Chemistry Group, Chemical Science and Technology Division, CSIR-NEIST, Dr. P.J. Bhuya and the entire scientific staff for their constant encouragement.

The project would not have been possible for me without the help and support of Limi ba, Kashmiri ba, Aswini da, Avilash da and Kumud da. I have been very fortunate to be around very pleasing and helpful people who were always there to help me in any kind and make me feel comfortable in a completely new environment.

Last but not the least, I would take the opportunity to thank my parents for their innumerable support through everything I do.

Chayanika Dutta.

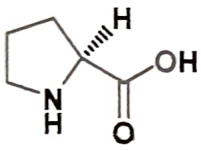
CONTENTS

ABBREVIATIONS USED

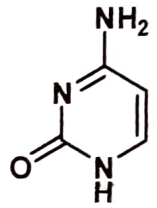
1. DCM : dichloromethane
2. DMF : dimethylformamide
3. Et : ethyl
4. g : gram
5. h : hour
6. TLC : Thin layer chromatography
7. Me : methyl
8. Min : minute
9. mg : miligram
10. mol : mole
11. IR : infrared
12. NMR : nuclear magnetic resonance
13. R_f : Retension Factor
14. Hz : Hertz
15. MHz : Mega Hertz
16. ^{o}C : Degree centigrade

GENERAL INTRODUCTION

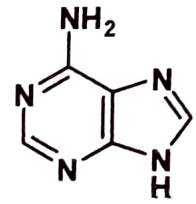
The main focus of this project is the synthesis of β-chloro-α,β-unsaturated aldehyde as intermediate which could be used as a synthon for various heterocycles. Most of the biologically active compounds are comprised of heterocycles, many of which are employed in regular chemical practice. The heterocyclic compounds are widely distributed in nature and play a vital role in the metabolism of all living cells. Some of these are natural products; for example, antibiotics such as penicillin, cephalosporin; alkaloids such as quinine, morphine and reserpine etc.



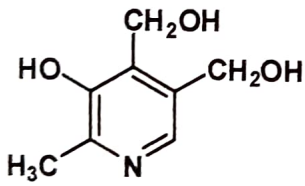
Proline



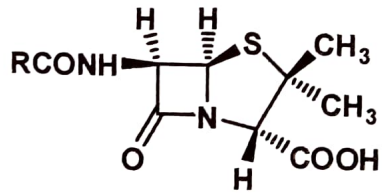
Cytocine



Adenine



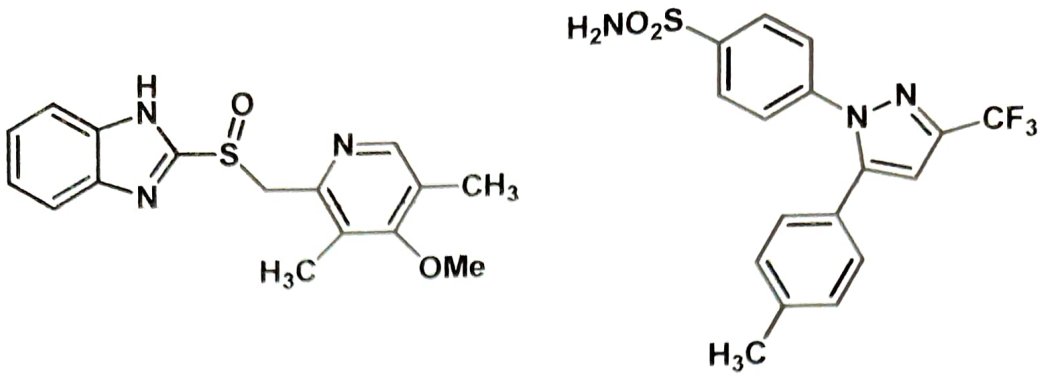
Vit B_6



Penicillin

Fig 1: Structures of some biologically important molecules containing heterocyclic ring

In addition, synthetic heterocyclic compounds are also found in various drugs and they exhibit various activities such as anticancer agents, hypnotics, modifiers, veterinary products, agrochemicals etc.



Omeprazole(antiulcurative)

Celecoxib(antiarthritic)

Fig 2: examples of some drugs containing heterocyclic ring

The β-halo aldehydes are very interesting compounds, which could be transformed to various fused heterocycles by using the reactivity of halide for nucleophilic substitution in combination with the various possibility of transformation of aldehyde functionality. Some examples of β-chloro- α, β- unsaturated aldehyde are shown in Fig 3.

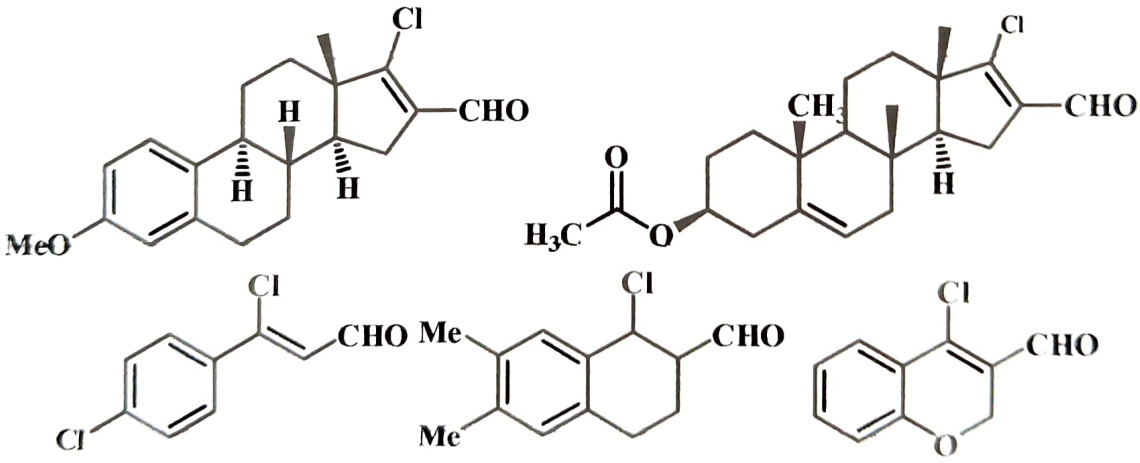


Fig 3: Examples of some β-chloro- α,β- unsaturated aldehydes

β-Chloro- α,β-unsaturated aldehyde (chloroformyl): The β-chloro- α,β-unsaturated aldehyde (chloroformyl) has been explored as synthetic synthon for different heterocycles as shown in fig 4. They have been used for the synthesis of various heterocycles such as pyridine, pyrimedines, thiophene, furan, coumarin etc.

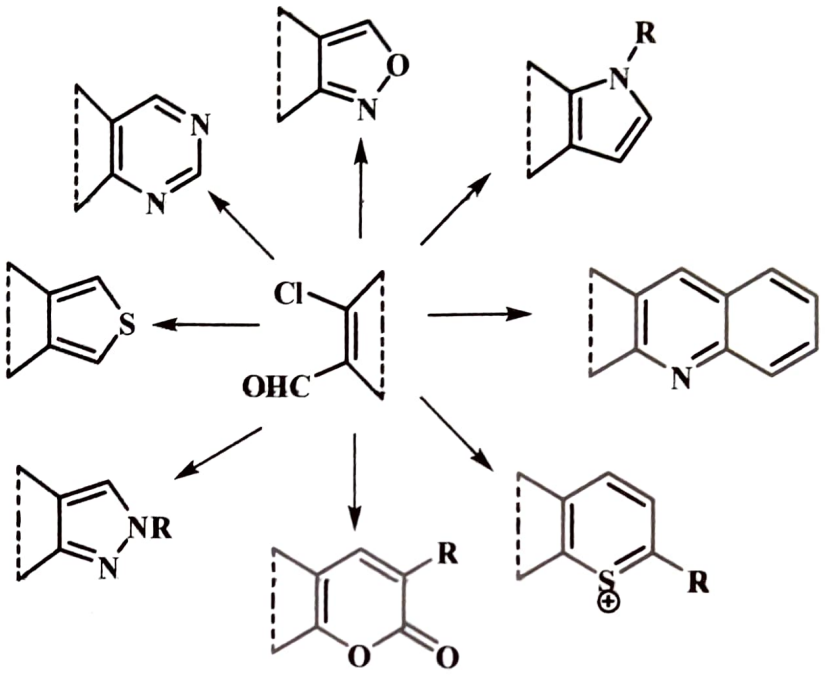
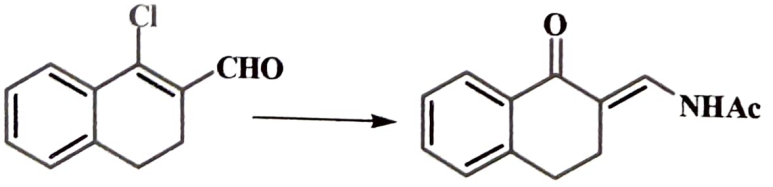


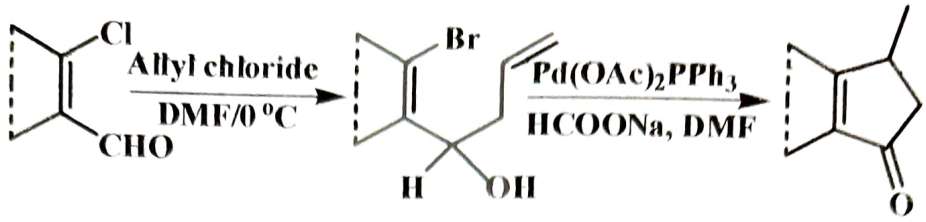
Fig 4: Some synthetic applications of β-chloro- α,β-unsaturated aldehyde

SOME SYNTHETIC APPLICATIONS OF CHLOROVINYL ALDEHYDE:

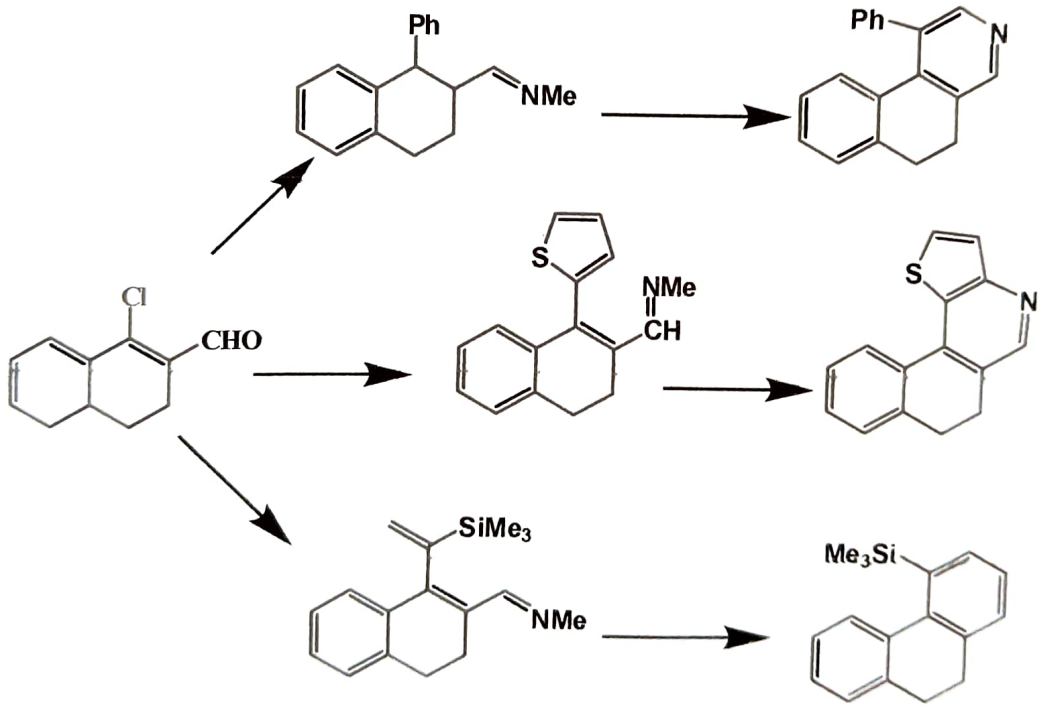
1. **Synthesis of β-ketoenamide:** **1-Chloro-3,4-dihydronapthalene-2-carboxaldehyde can be used as starting material for the synthesis of ketoenamide.**



2. **Synthesis of cyclopentanone containing fused rings:** Fused carbocycles can be synthesized from chlorovinyl aldehyde.

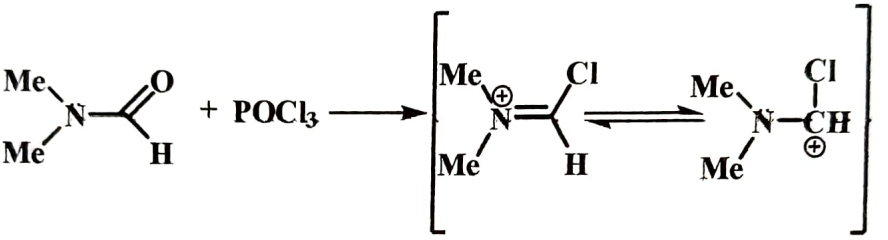


3. **Synthesis of 5,6-dihydrobenz isoquinoline:** Using 1-chloro-3,4-dihydronapthalene-2-carboxyaldehyde as starting materials, 5,6-dihydrobenz isoquinolines can be synthesized.



VILSMEIER-HAACK REACTION

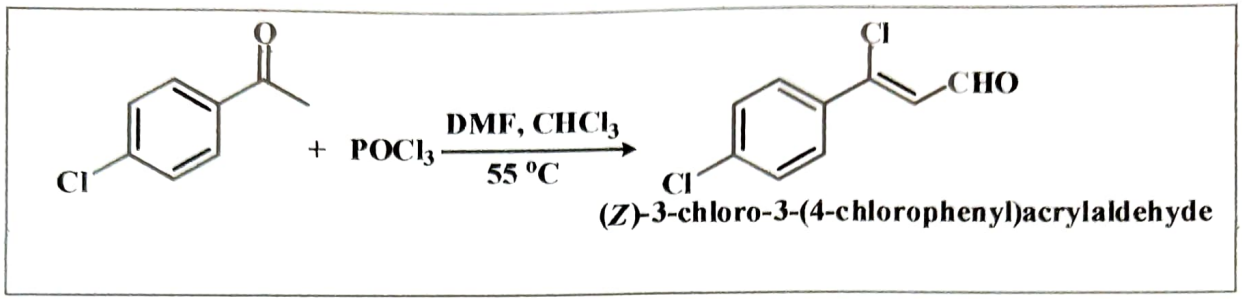
The Vilsmeier- Haack reaction (also called the Vilsmeir reaction) is the chemical reaction of a substituted amide with phosphorous oxychloride and an electron-rich arene to produce an aryl aldehyde or ketone. In 1927, Vilsmeier and Haack discovered that N,N-dimethylformamide formylated aniline derivative in presence of phosphorous trichloride. The classical Vilsmeier Haack reaction involves electrophilic substitution of a suitable carbon nucleophile with a chloromethyleneiminimum salt. Chloromethyleneiminimum salt is prepared by treating DMF with $POCl_3$, at a low temperature.



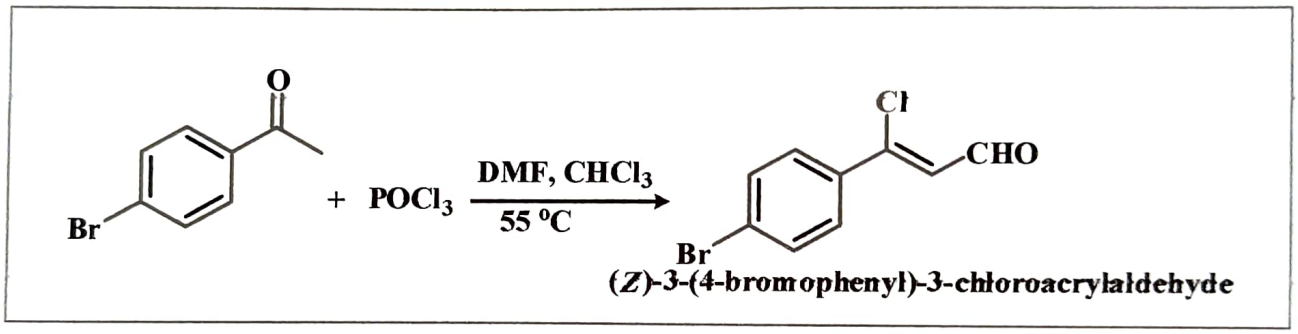
Vilsmeier reaction is one of the most widely used reactions especially for formylation of various organic substrates in organic chemistry. It plays an important role in the conversion of organic compounds into its corresponding chlorovinyl aldehydes.

Due to the importance of chlorovinyl aldehydes in synthesis of various organic compounds, it is important to synthesize these compounds. Therefore, I have synthesized some chlorovinyl aldehydes using various acetophenones as starting materials.

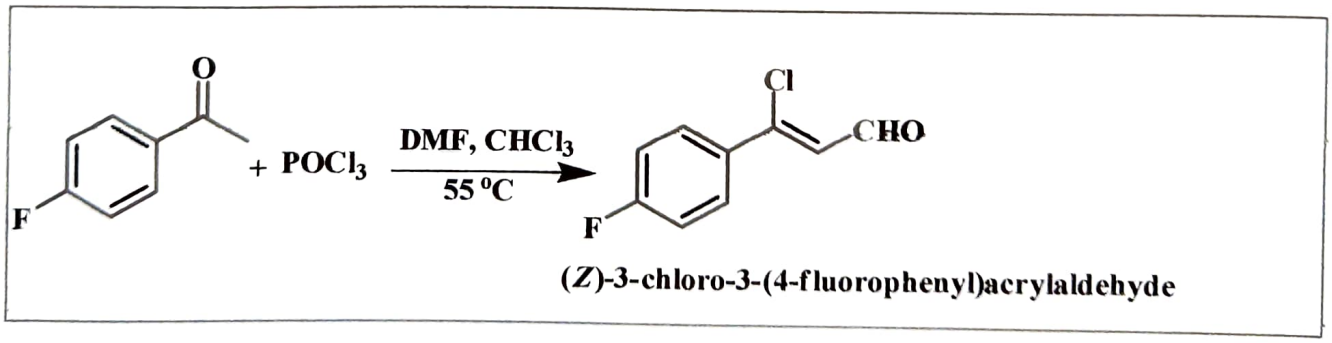
Scheme 1: Preparation of (Z)-3-chloro-3-(4-chlorophenyl)acrylaldehyde from 4′ chloroacetophenone.



Scheme 2: Preparation of (Z) -3-(4-bromophenyl)- 3-chloroacrylaldehyde from 4′-bromoacetophenone.



Scheme 3: Preparation of (Z)-3-chloro-3-(4-flurophenyl)acrylaldehyde from 4′-Fluroacetophenone.



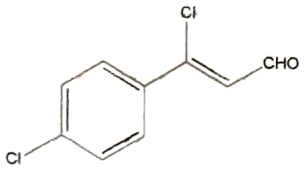
General procedure for the preparation of β-chloro- α,β-unsaturated aldehyde:

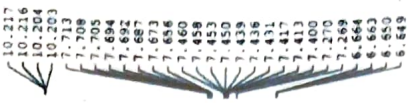
A solution N, N-dimethylformamide (0.7 ml, 10 mmol) in anhydrous chloroform (15 ml) was cooled in ice bath. Phosphorous oxychloride (0.46 ml, 5 mmol) was added drop-wise over a period of 10 minutes. The resulting white suspension was warmed to room temperature and stirred for another 30 minutes. A solution of acetophenone (0.13 ml, 1 mmol) in chloroform (15 ml) was added drop-wise and the reaction mixture was refluxed for three hours. The reaction mixture was then poured into ice water. $NaHCO_3$ was carefully added to neutralize the acids and the mixture was extracted with chloroform (three times). The organic part was then washed with cold water followed by dried over sodium sulphate. The crude was purified using column chromatography [silica gel (60-120 mesh)]

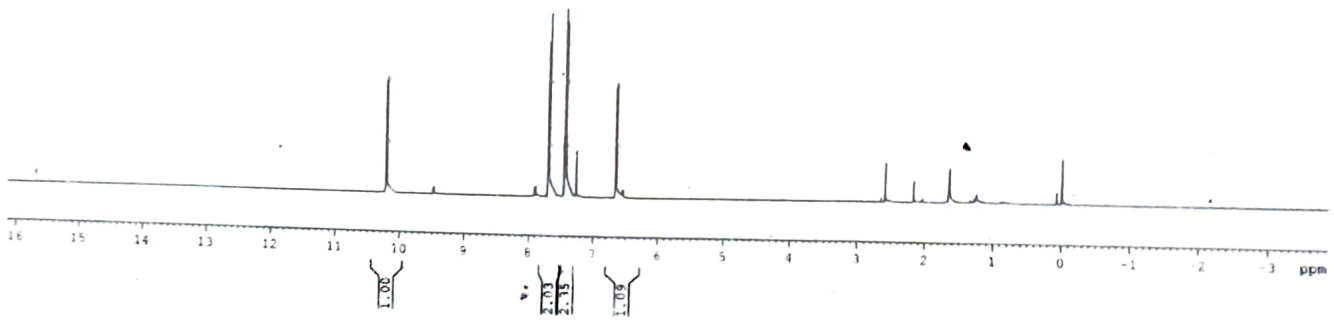
RESULTS AND DISCUSSION

(Z)-3-chloro-3-(4-chlorophenyl)acrylaldehyde: Yellow solid, mp:89.5-89.7°C; yield = 94.64% , R_f = 0.51 (5% EtOAc in hexanes). ^{1}H NMR (300 MHz, $CDCl_3$): δ =7.40 (s , 1H) ; 7.45 (s , 1H) ; 7.46 (s , 1H) ; 7.67 (s ,1H) ; 7.68(s , 1H) ; 10.203 (s ,1H), ^{13}NMR (75 MHz,$CDCl_3$): δ= 191.17,130.79,138.04, 128.79, 124.43. IR($CHCl_3$): 1668.6, 1588.3, 1487.9, 1219.9, 1139.0, 1094.4, 817.3, 772.2, 665.8 cm^{-1}.

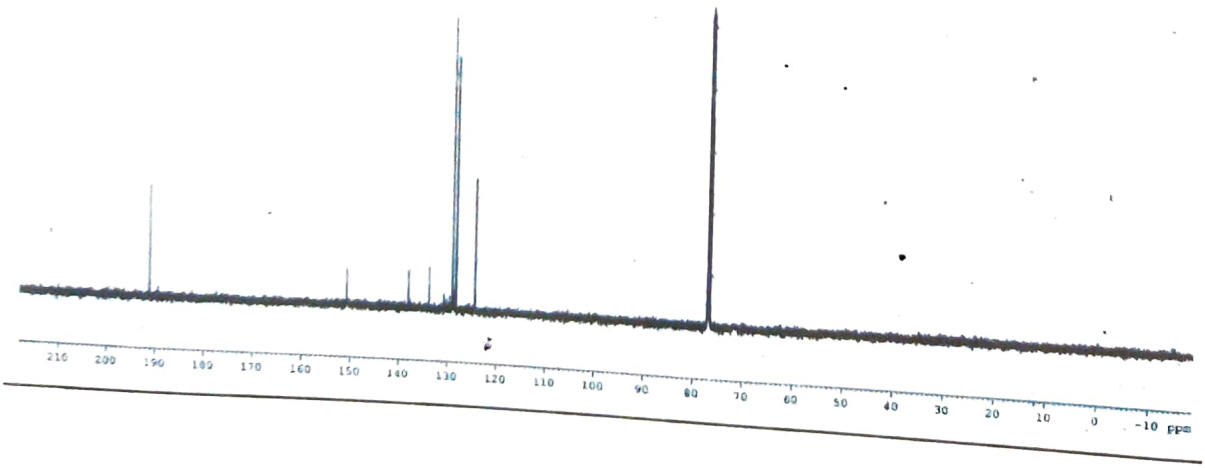
15368
CD-1







Name of Sample:CD-1
Spectrum No :15369



CONCLUSION

We have synthesized some β-chloro-α,β-unsaturated aldehydes using various substituted acetophenones. All the products were isolated with satisfactory yields and characterised by ^{1}H and ^{13}C NMR. The synthesized β-chloro-α,β-unsaturated aldehydes could be used as intermediates for the synthesis of various heterocyclic compounds.