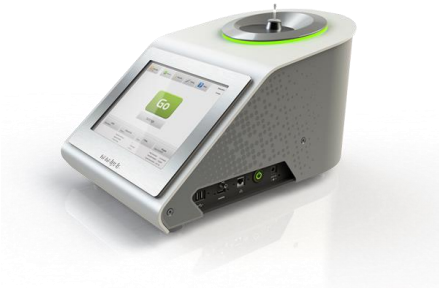

60MHz NMR Nanalysis Instrument. MCC

NEW METHODOLOGY ATTEMPTED FOR THE SYNTHESIS OF CHLORAMPHENICOL

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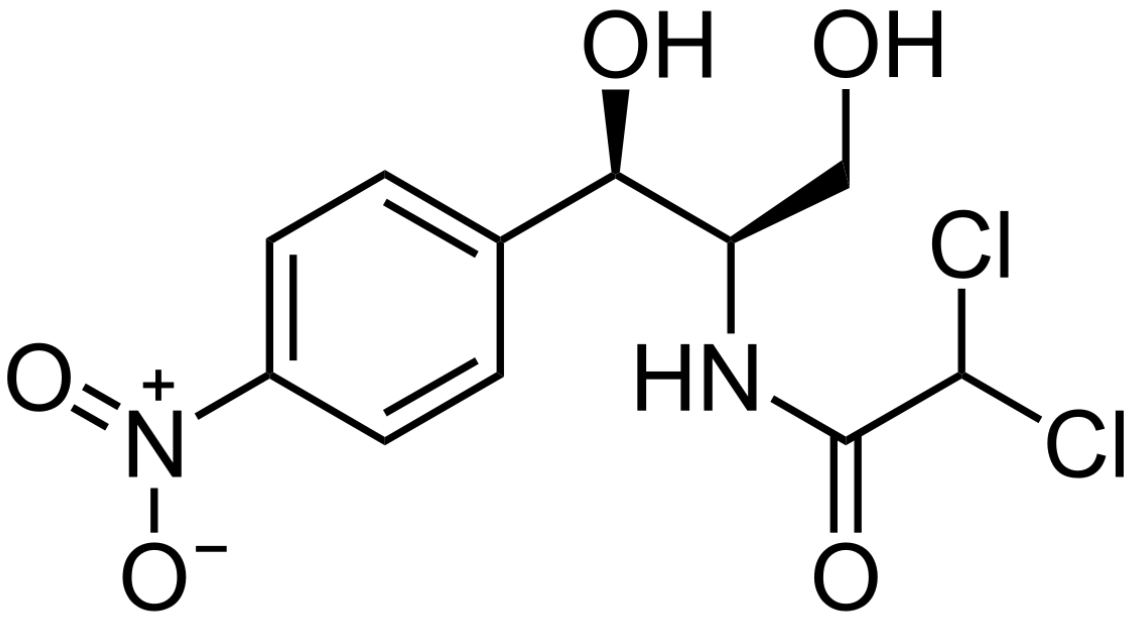
Abstract

A new synthetic method for preparation of the antibiotic drug, Chloramphenicol, was proposed. The earlier methods of producing the drug involves utilization of hazardous chemicals. The motive was to find a synthesis method was to utilize as much as non-hazardous materials to prepare the drug. The goal was to optimize the conditions for the adoptions of the methodology in industrial scale. The hypothesis involved using enantioselective catalysts-Diphenyl Prolinol for Michael addition of p-Nitrobenzaldehyde and the amino group. The hypothesis suggests a yield of over 90% of the desired isomer. The Aminodiacetylaldehyde dimethyl acetal was first reacted with Dichloroactyl chloride. The product was then deprotected and further reacted with p-Nitrobenzaldehyde in the presence of the catalyst. Further the desired isomer was reduced with Sodium Borohydride. The expected product obtained would be cis isomer of the required molecule. Further, the molecule would be tested for its antibiotic properties.

MOLECULE OF INTEREST: CHLORAMPHENICOL

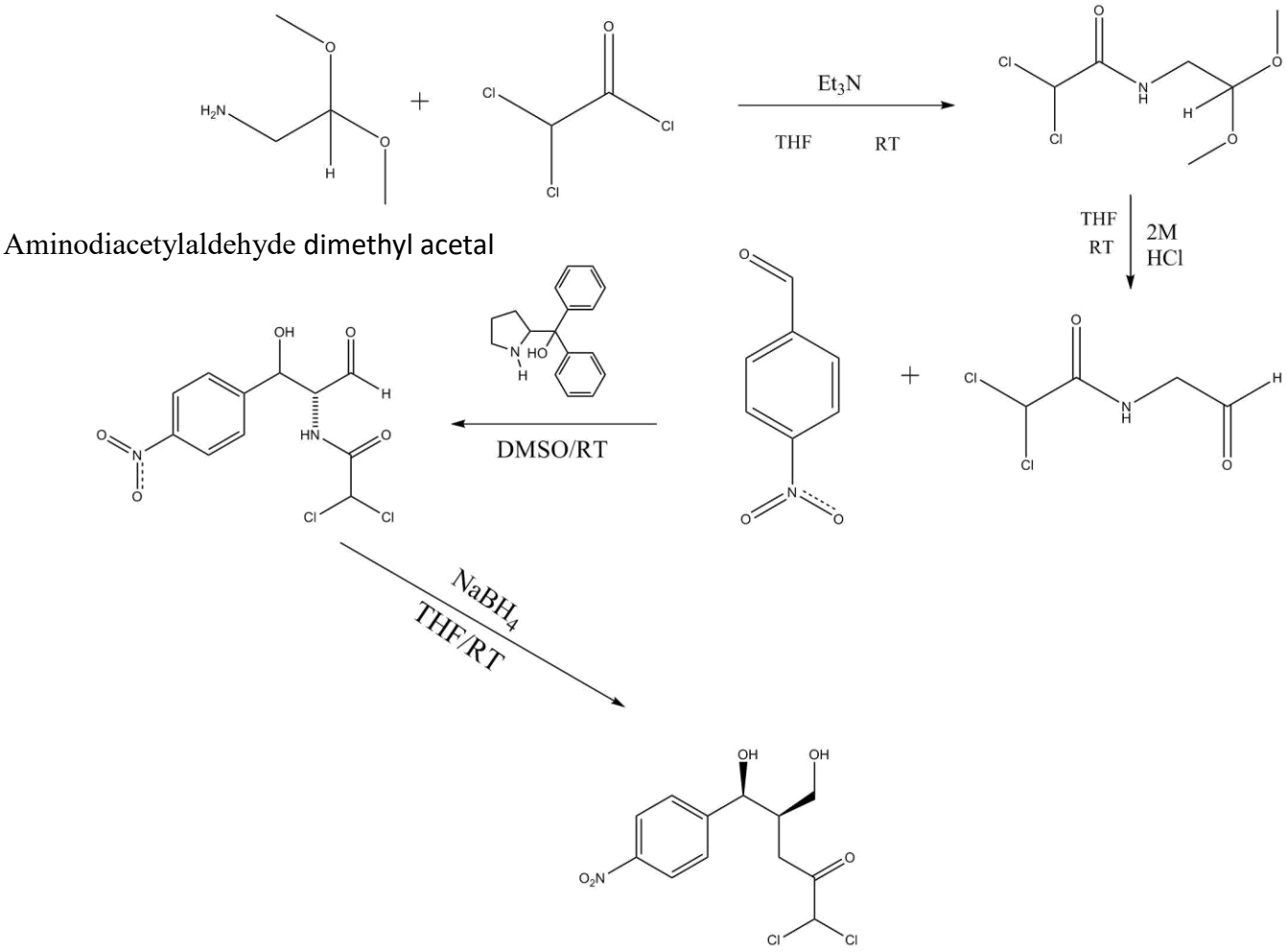


Objective

Chloramphenicol is an optically active molecule that has 2 chiral carbons (*) and 4 different stereoisomers. The only molecule of chloramphenicol that is biologically active is the one that has both of this chiral carbons in absolute configuration "R"(as shown above) . Since one of the reactants, the p-nitrobenzaldehyde, possesses a trigonal planar geometry, it will be attacked from both sides during the aldol reaction producing the aforementioned stereoisomeres. (xxxx add) Resulting in a very wasteful reaction.

To address this issue, previous experiments conducted by a student at MCC, who used proline as a catalyst, (xxx) as it favors the production of the chloramphenicol that is biologically active. The present approach is to use of the substituted proline (diphenylprolinol) as catalyst which could have much better impact on the reaction, and increase the production of the target molecule over its stereoisomers. Similar synthetic routs has been reported[4] for other aldol reactions. The proposed synthetic scheme for synthesizing chloramphenicol is given below:

2,2-dichloro-N-(2,2-dimethoxyethyl)acetamide



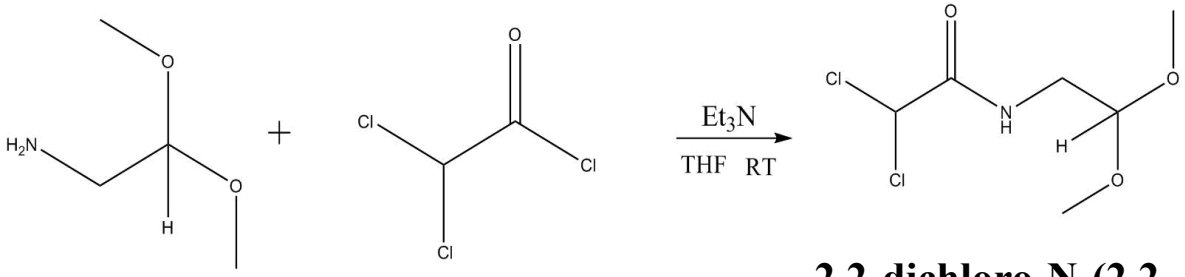
Aminodiacetylaldehyde dimethyl acetal

Chloramphenicol

THE SYNTHESIS of INTERMEDIATES

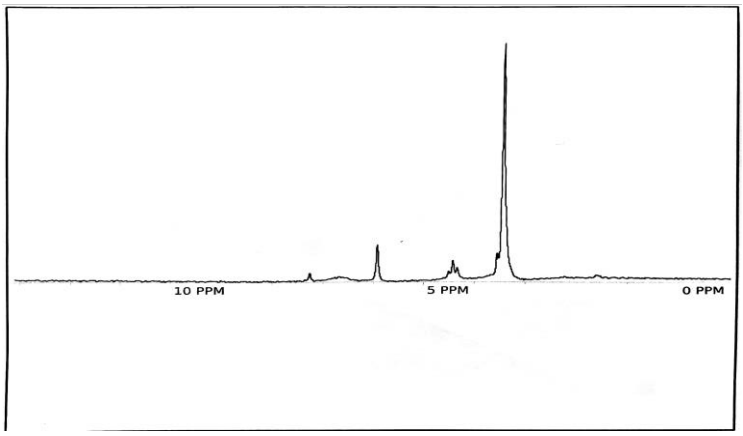
Step 1- Acylation- Adding Acyl

Dichloroacetyl chloride

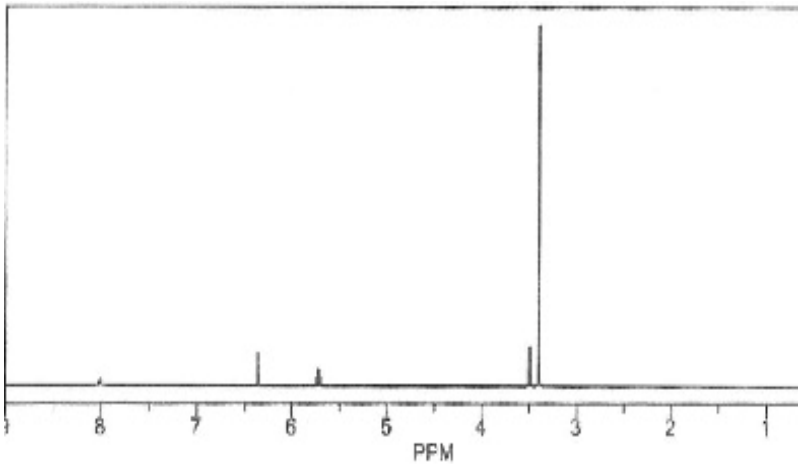


Aminodiacetylaldehyde dimethyl acetal

2,2-dichloro-N-(2,2-dimethoxyethyl) acetamide

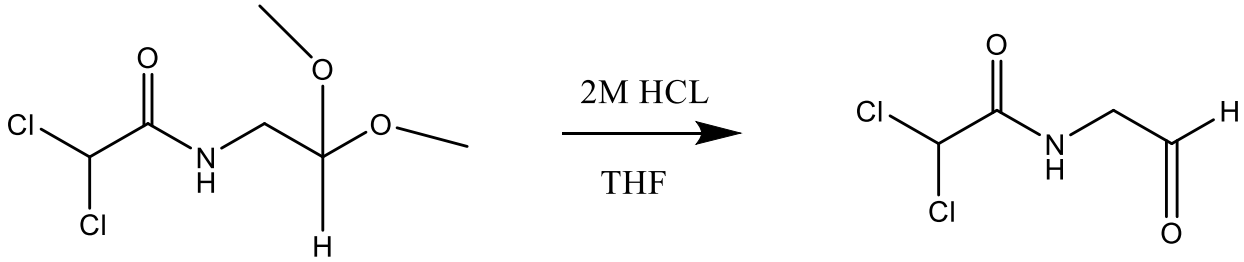


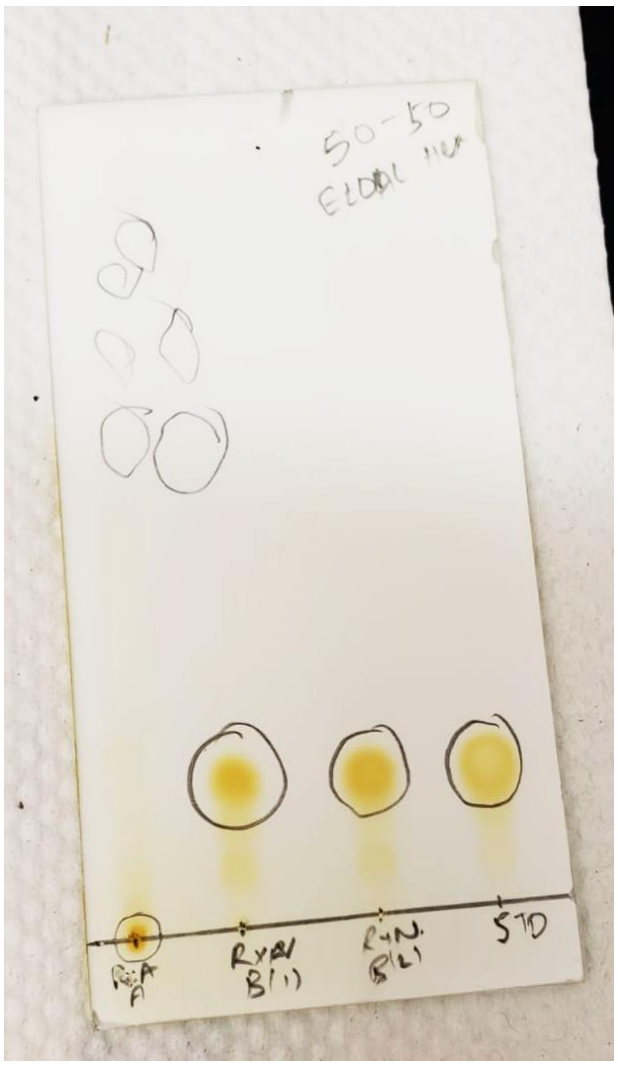
NMR taken in CDCl3



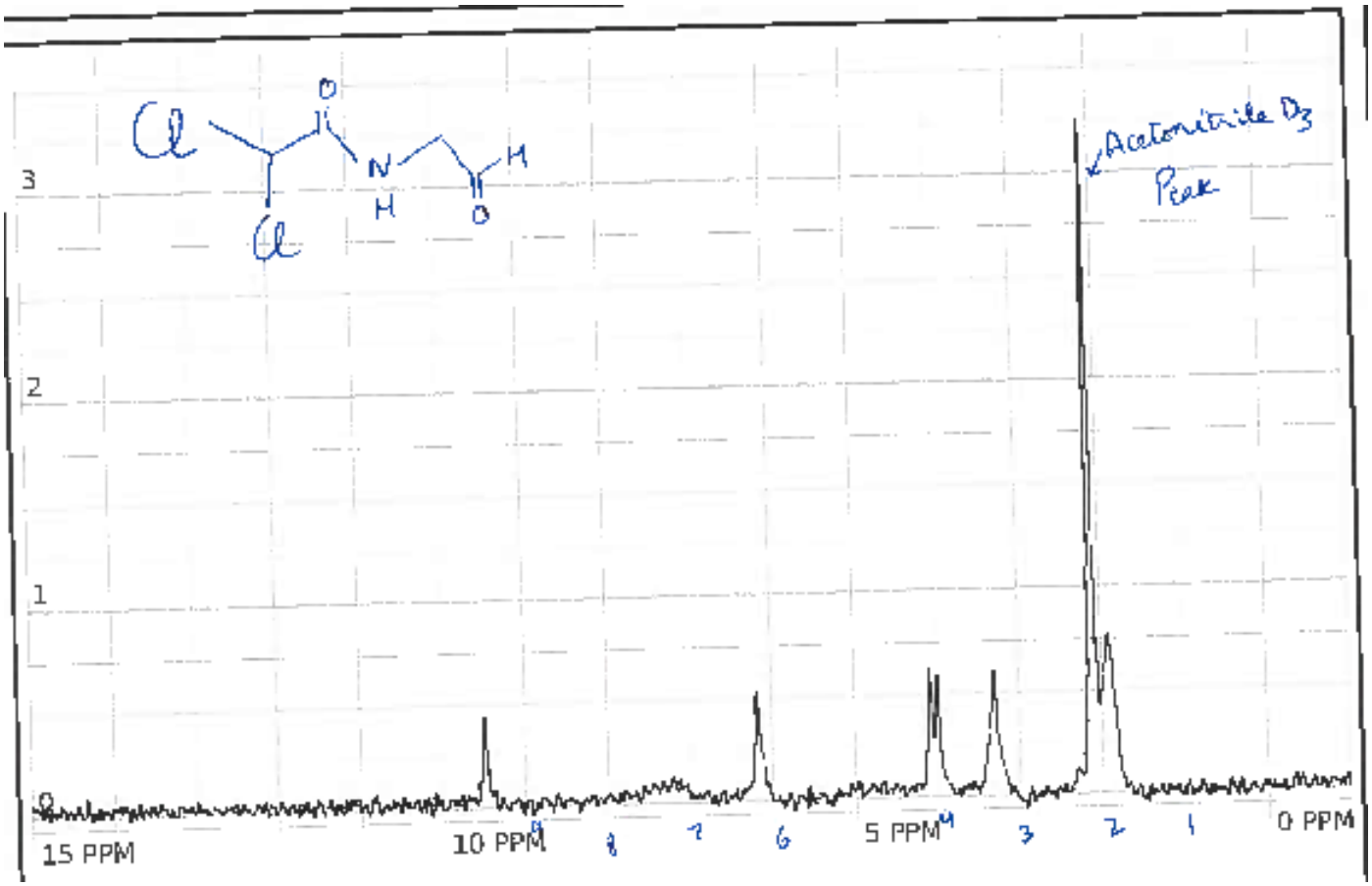
Chem.-Draw NMR in DMSO

Step 2- Hydrolysis of the Di-Acetyl group

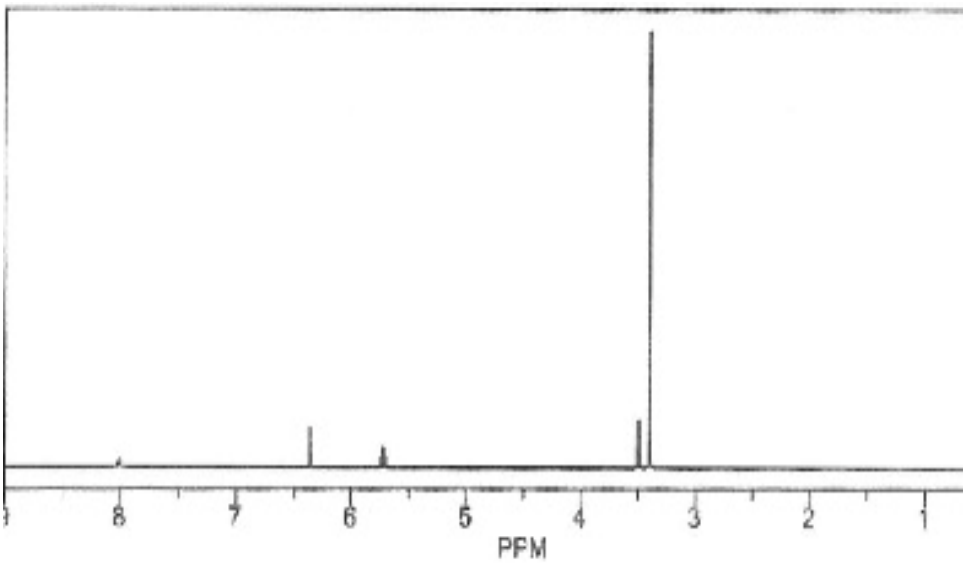




- The Product was further checked on the TLC plate with solid phase as SiO2 .F254 and 50-50 Ethyl Acetate and Hexane .
- As the compound has no Chromaphores, it was put in an Iodine developing Chamber.
- It was compared to the previous attempt and ran with the step 1 to check any of the starting material leftover. The plate showed no remaining starting material and was observed

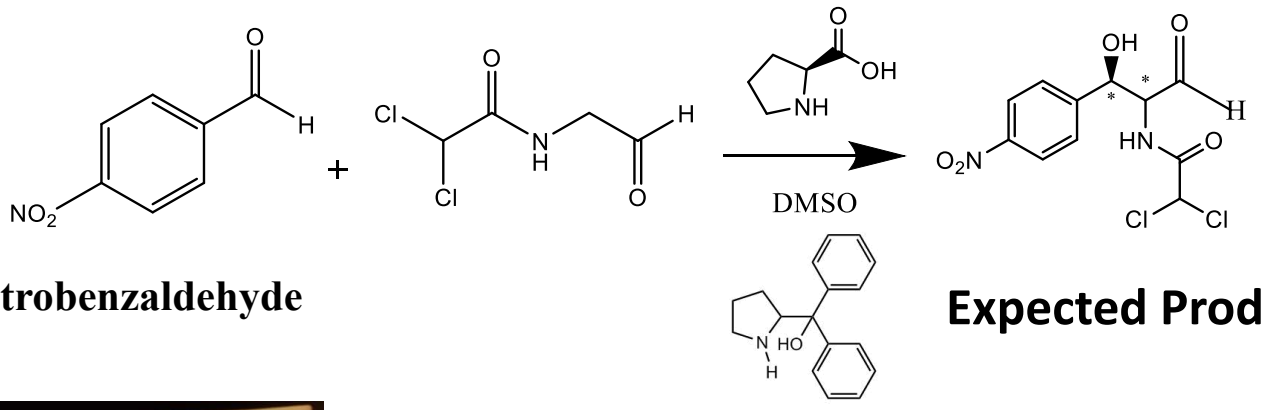


NMR taken in Acetonitrile - ^{3}D



Predicted NMR in ^{6}DMSO

Step 3- Michael Additions using Diphenyl Prolinol as a catalyst



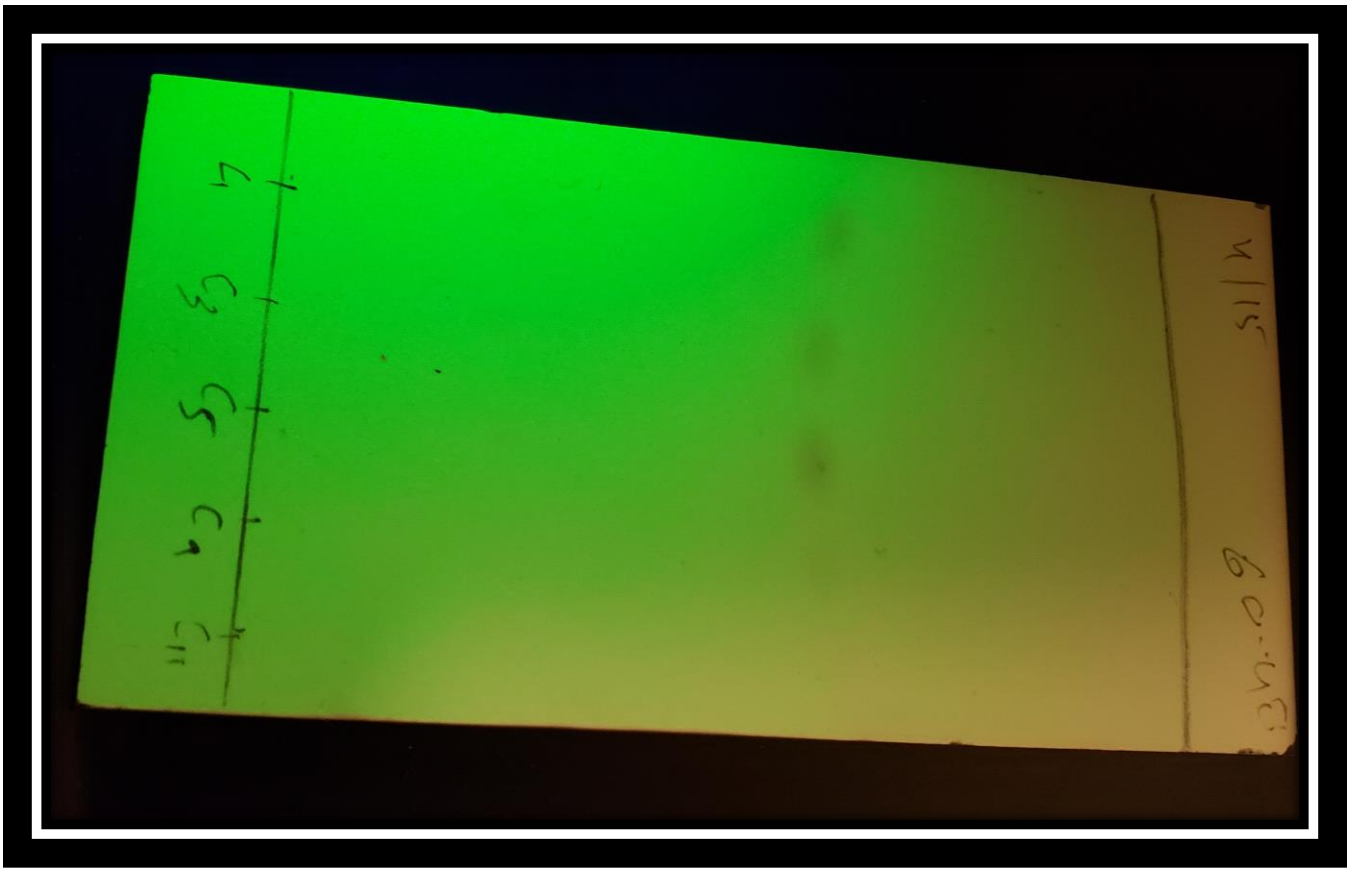
p- Nitrobenzaldehyde

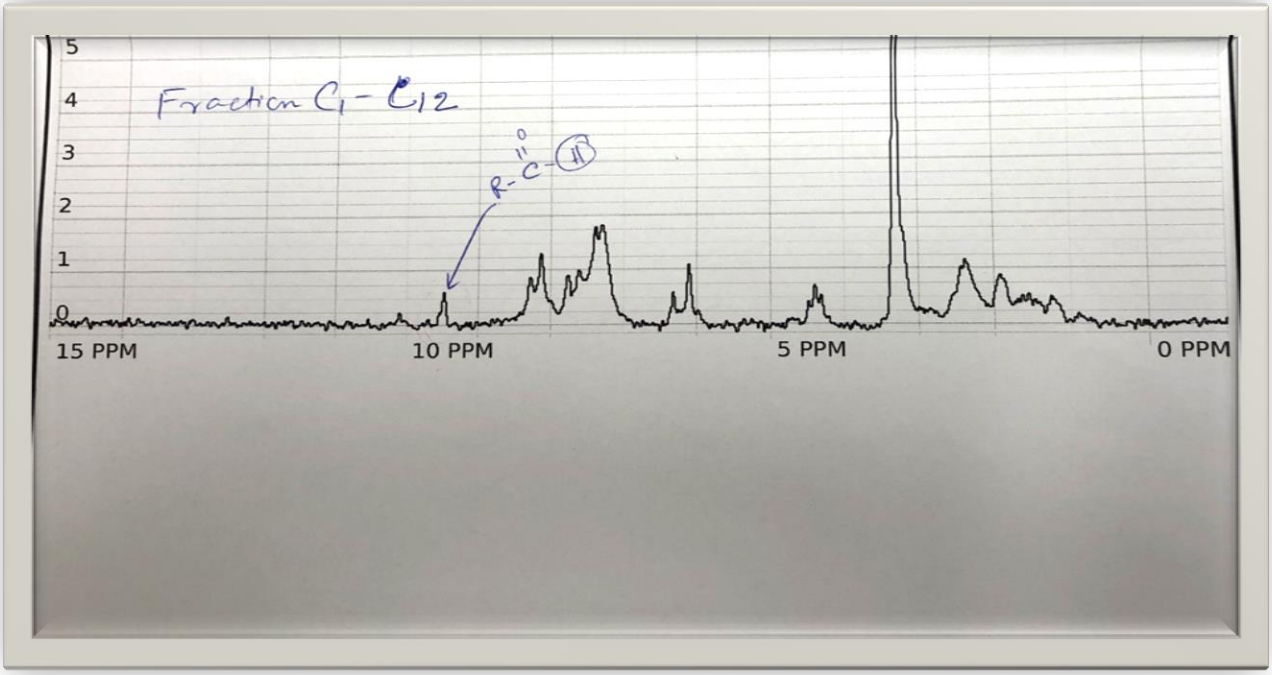
Expected Product

Toluene/Water

- The TLC showed still a lot of unconsumed p-Nitrobenzaldehyde. The workup steps appeared to have got rid most of the catalyst.
- The Sample was the then transferred into a column to separate the excess of Nitrobenzaldehyde.
- I tried to separate out the compound in red.

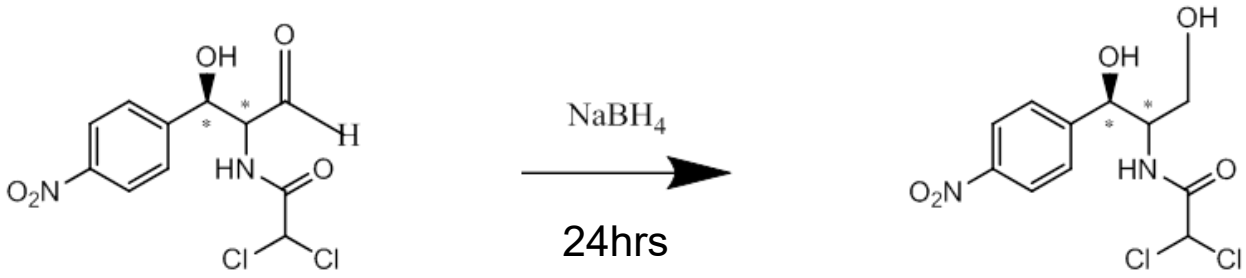
- The separation was started with 100% Hexane
- The solution was then made slowly polar from 5-95% EtOAc-Hexane and further till 40-60% EtOAc.
- In total **I took about 50 fractions**, out of that 12 **(C1-C12)** were separated which had no p-Nitrobenzaldehyde.
- There were some fractions from what appears to have another product but no starting materials, like p-Nitrobenzaldehyde. I separated and stored that fractions too for further analysis.



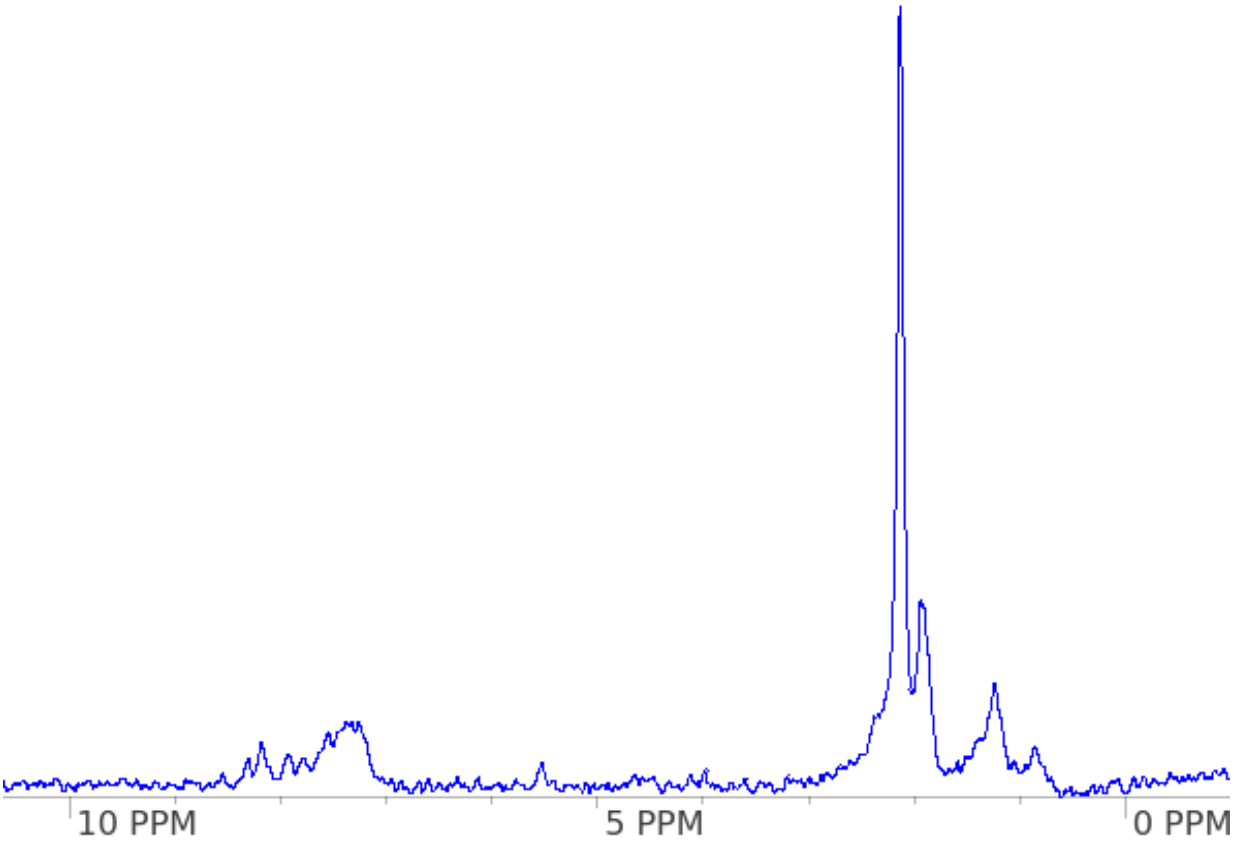

5
4
3
2
1
0
Fraction C1 - C12
R-C=O
15 PPM
10 PPM
5 PPM
0 PPM

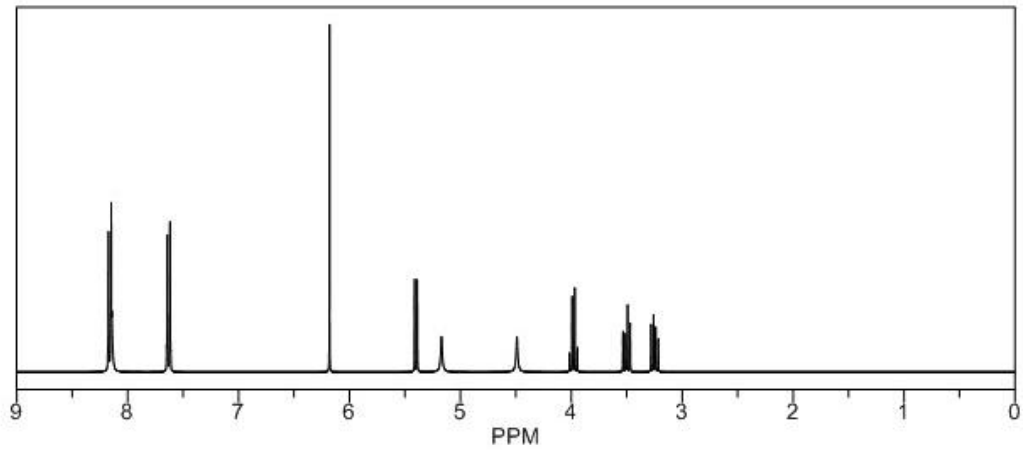
NMR of the Aldol Product

Step 4- Reduction of aldehyde with Sodium Borohydrate



Expected product: Chloramphenicol





This was the NMR for the final product obtained during fall 2018. The Product obtained after the column chromatography done twice and drying out, was too small. In this product, at least we do not see any aldehyde proton around 10 ppm! So, we hypothesized it could be the reason the NMR was not showing all the resolved peaks.

FUTURE WORK

Optimization of the reaction for perfect conditions to get higher yield so that the NMR is possible.

Find a correct solvent solution to elude all nitrobenzaldehyde out from step 3.

My goal is to establish the proof of concept and establish the methodology which is yet to achieve.

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