TITLE: Synthesis of Amino-Aldehydes from Activated Amino Acids

By

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CHM 240 (Research in Chemistry)

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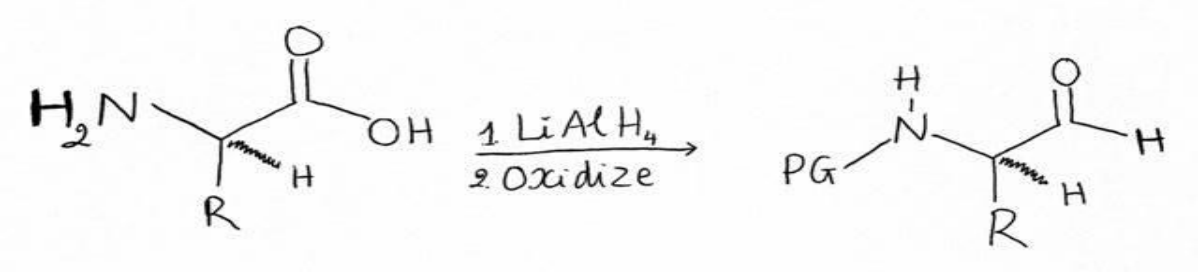
ABTRACT:

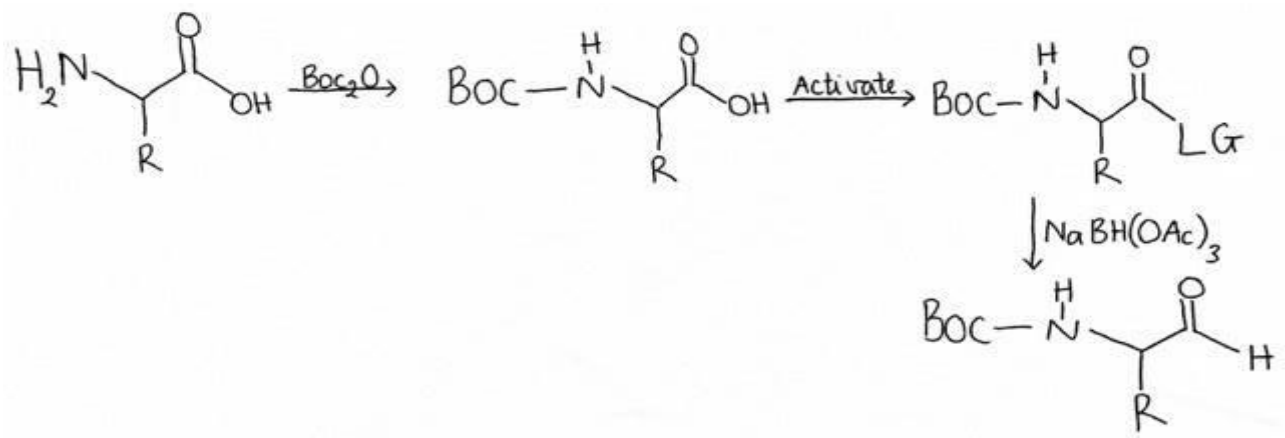
A method for the synthesis of Amino-Aldehydes starting from natural amino acids is reported. Glycine and Di-tert-butyl dicarbonate (Boc2O) were prepared through the reaction of protected amino aldehydes obtained from starting material. In the first part of this project, we explored the direct reagent reaction between Glycine and Boc is 1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC). The reaction was set under normal condition and room temperature. When reacting with $NaBH(OAc)_3$, we got the final product. Detail characterization of a product was determined by TLC and NMR. In the second part of this project, we explored the stronger reagent reaction by using Pivaloyl Chloride instead of EDC. We got an unknown compound, and we could not identify the structure of this compound until we took NMR. In the third part of this project, we explored the strongest reagent reaction by using Tosyl Chloride instead of EDC and Pivaloyl Chloride. We got the unknown compound products, then took an unknown product to react with methanol and NaBH(OAc)3 to get the final product. We got an unknown compound, and we could not identify the structure of this compound until we took NMR.



INTRODUCTION:

Amino acid is a simple organic compound containing both a carboxyl (—COOH) and an amino (—NH2) group. Amino acids are at the basis of all life processes, as they are absolutely essential for every metabolic process. The project contains three steps. First step, we need to protect

Amino Acids by using Di-tert-butyl dicarbonate (Boc2O) that is a reagent widely used in organic synthesis. Seconds step, we will be activating the amino acid by some reagents such as EDC, Pivaloyl Chloride, or Tosyl Chloride. Third steps, we will reduce the amino acid by using NaBH(OAc)3 to remove the leaving group. Remember step 2 and 3 are done in the same reaction flask. The goal of the project is to synthesiz successfully the Amino Aldehydes from Amino acids. Amino-aldehydes are used in the synthesis of biologically active compounds.

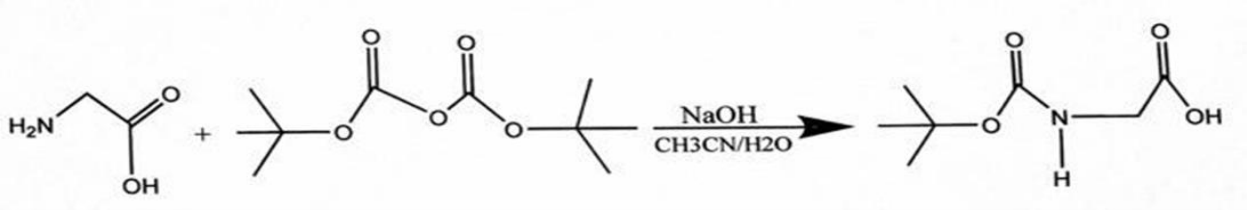


Experimental Section:

Instrumentation: TLC plate was used to check research material with starting material. NMR spectra were recorded using NMRReadyTM 60 Analysis Corporation. D-chloroform was used as a reference/ blank and also as solvent for all compounds. D2O was used for identify – NH proton group.

Materials: All materials used for preparation were reagent graded and used without further purification. TLC plate was used Column Chromatography with silica gel as stationary phase and Ethyl alcohol/ Ethyl acetate(9.5:0.5) as mobile phase.

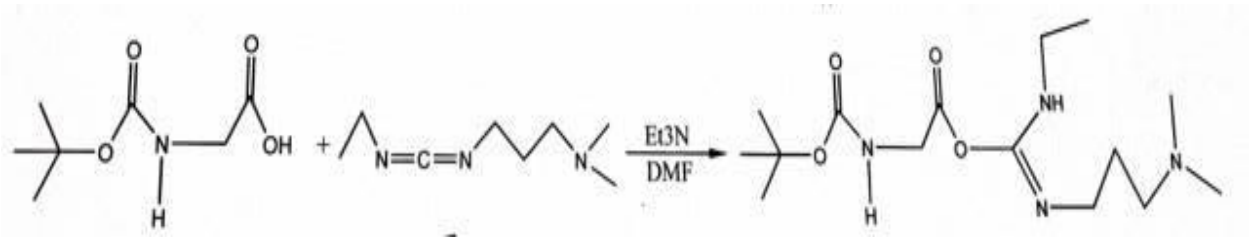
Step 1: Protect the amino acid



- ✓ In a 100 ml round-bottomed flask weigh 1.5 g of glycine, add 4.5g of Boc2O, add 0.9g of NaOH, add 15ml H20, and 15ml CH3CN, add magnetic stir bar and gently swirl the mixture.
- ✓ Then closed by septum and stirred overnight.
- ✓ Then collected the white solid product
- ✓ Took a small product to run TLC
- ✓ Then work-up with some organic method such as extraction, rotary evaporation, and vacuum.
- ✓ Final took NMR with 1.5ml D-chloroform.

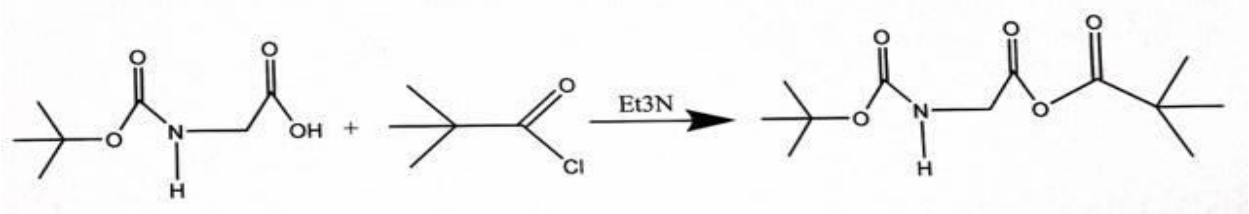
Step 2: Active the amino acid by reagents

- ✓ With EDC:



- ✓ In a 100 ml round-bottomed flask weigh 270mg of Boc Glycine. Add 300mg of EDC, add 240ul of trimethylamine, and add 9ml dimethylformamide (DMF), add magnetic stir bar. Then stirred 1 hour.

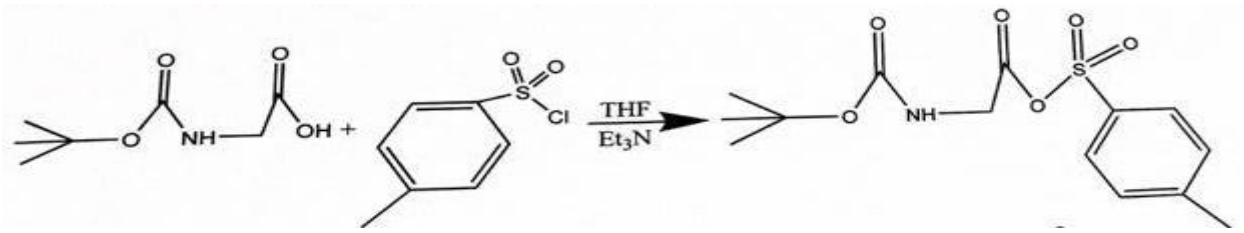
- ✓ With Pivaloyl Chloride:



- In a 100 ml round-bottomed flask weigh 300mg of Boc Glycine, add 270ul

Triethylamine, add 240ul of Trimethylacetyl Chloride, and 5ml ethyl acetate, add magnetic stir bar. Then stirred overnight.

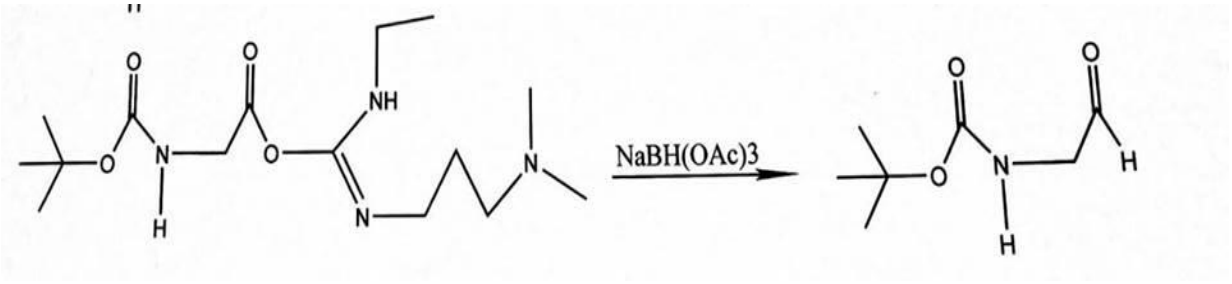
- ✓ With Tosyl Chloride:



- ✓ In a 100 ml round-bottomed flask weigh 300mg of Boc Glycine, add 5ml THF, add 300ul trimethylamine, add 360mg p-toluene sulfonyl chloride (Tosyl), and add magnetic stir bar. Then stirred overnight.

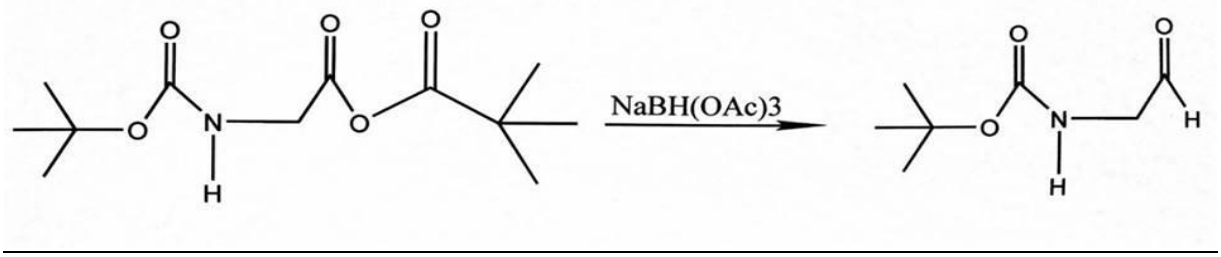
Step 3: Reduce the amino acid

- ✓ **With EDC**

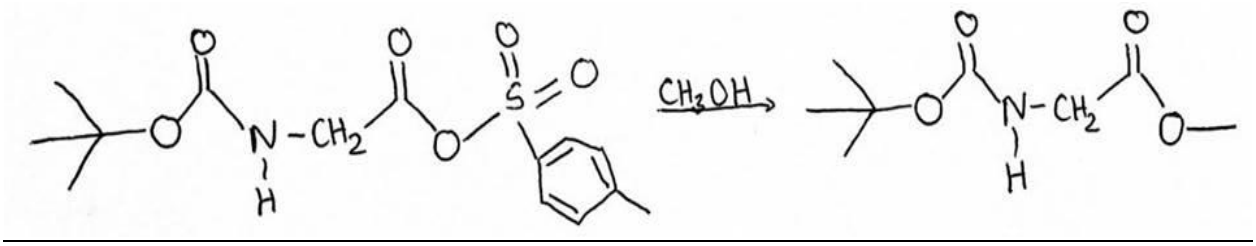


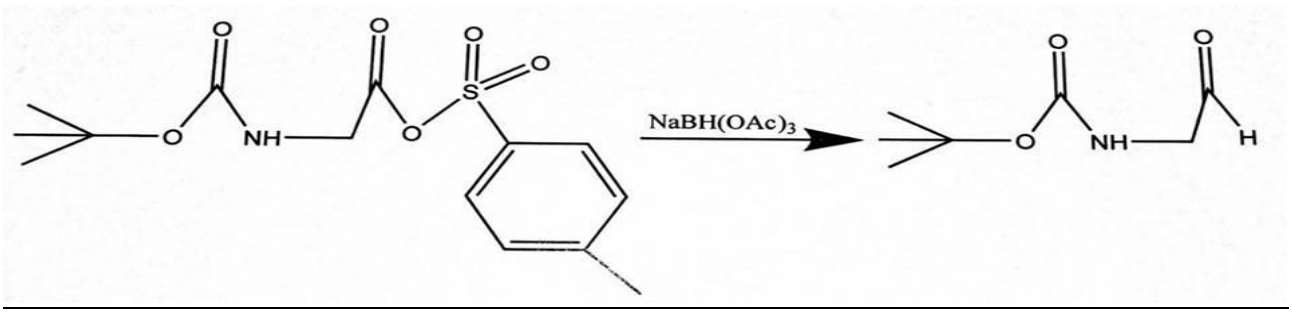
- ✓ After stirred 1 hour, add 360mg of NaBH(OAc)3, add magnetic stir bar. Then stirred overnight.
- ✓ Then got product.
- ✓ Took a small product to run TLC
- ✓ Then work-up with some organic method such as extraction, rotary evaporation, and vacuum.
- ✓ Final took NMR with 1.5ml D-choloroform to get data.

- ✓ With Pivaloyl Chloride:



- ✓ After stirred overnight, add 270mg of NaBH(OAc)3, add magnetic stir bar. Then stirred overnight.
- ✓ We got the final product.
- ✓ Then work-up with some organic method such as extraction, rotary evaporation, and vacuum.
- ✓ Final took NMR with 1.5ml D-chloroform to get data.
- ✓ With Tosyl Chloride:





- ✓ After stirred overnight, took a half of product reacted with CH3OH and a half of remain of product reacted with 400mg of NaBH(OAc)3, add magnetic stir bar. Then stirred 1 hour.

- ✓ We got the final product.
- ✓ Took a small ml of product to run TLC.
- ✓ Then work-up with some organic method such as extraction, rotary evaporation, and vacuum.
- ✓ Final took NMR with 1.5ml D-chloroform to get data.

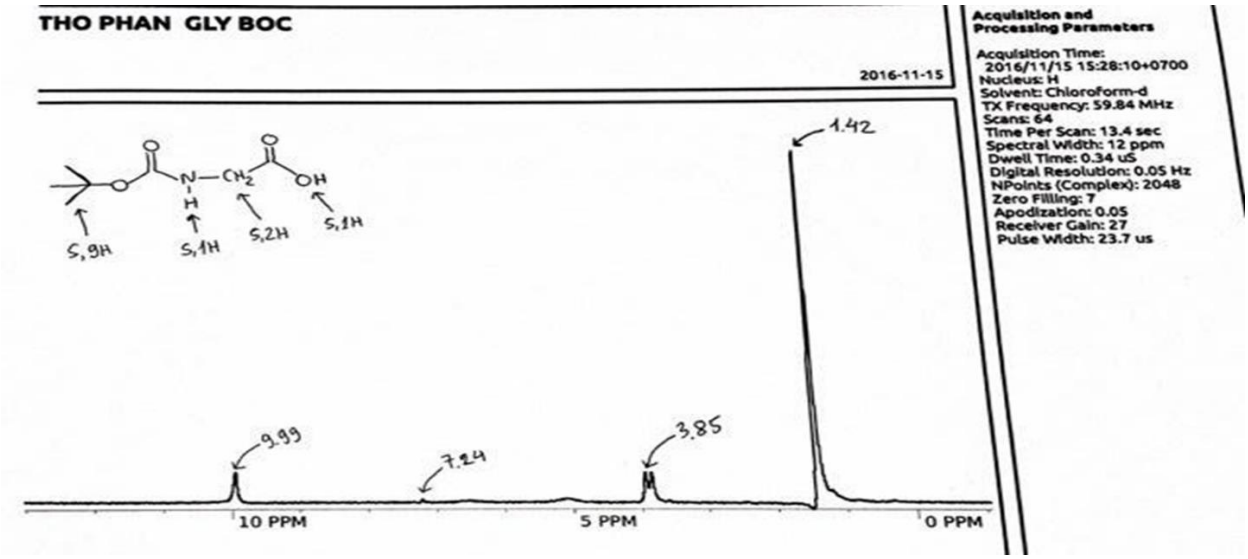
Result and discussion:

- ✓ **Step 1: Protect the amino acid**

- After purified the crude product using flask chromatography, the TLC plates showed:

The color of the spots on the chromatogram of testing samples corresponding to that of starting material compounds. Therefore, we can be concluded that Boc and Glycine is present.

- Then this product was dried out by Rotavap and characterized using NMR:



The peaks of testing samples corresponding to the peaks of starting material compounds. Therefore, we can be concluded that Glycine and Boc is present.

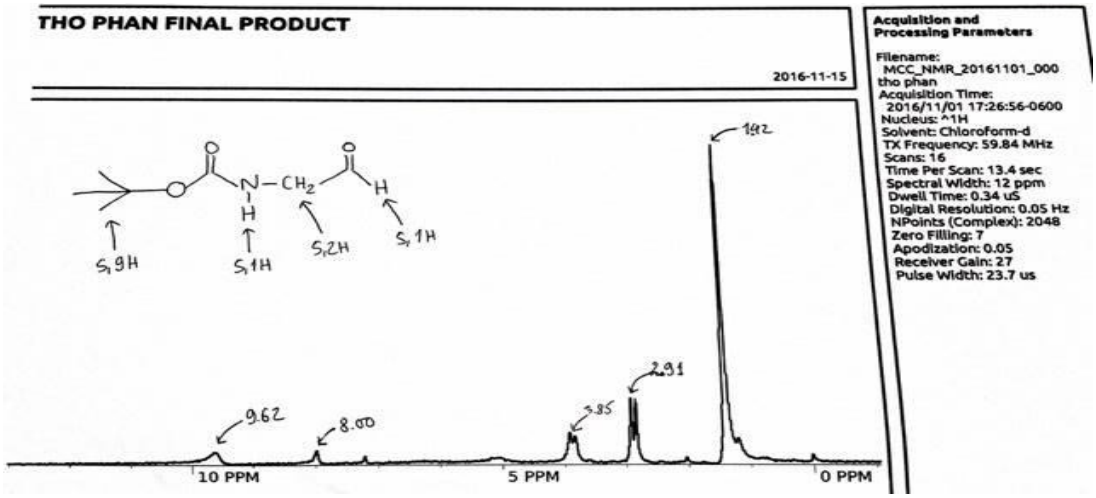
Step 2: Active the amino acid by reagents and Step 3: Reduce the amino acid

✓ With EDC:

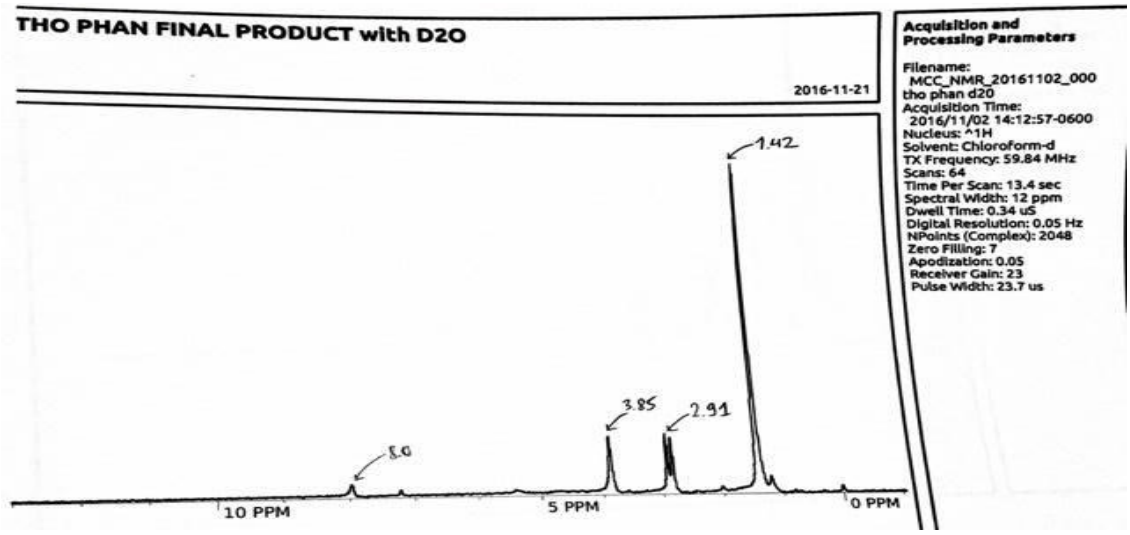
- After purified the crude product using flask chromatography, the TLC plates showed:

The color of the spots on the chromatogram of testing samples corresponding to that of starting material compounds. Therefore, we can be concluded that starting material is present.

- Then the final product was dried out by Rotavap and characterized using NMR:



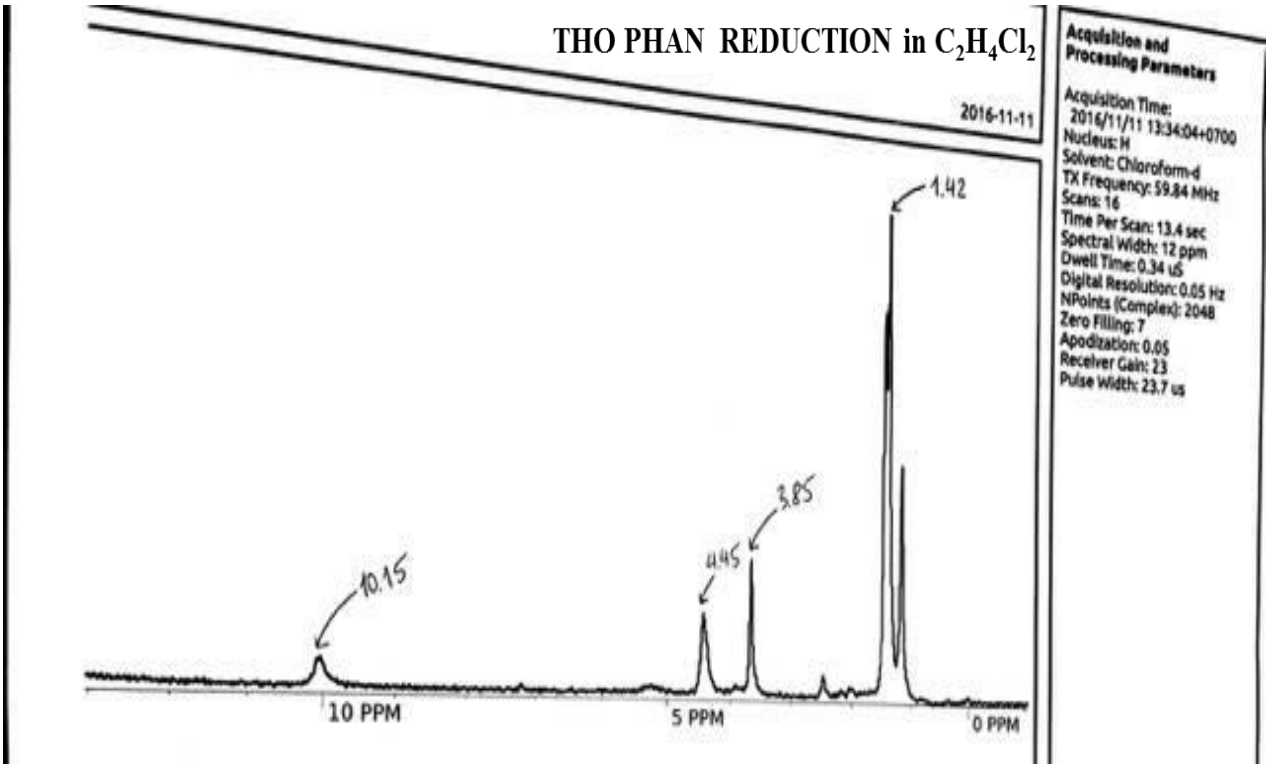
The some peaks of testing samples corresponding to the peaks of starting material compounds. But the peak of 9.62ppm is not sure that is aldehyde group or different group. Therefore, we tested with D20:



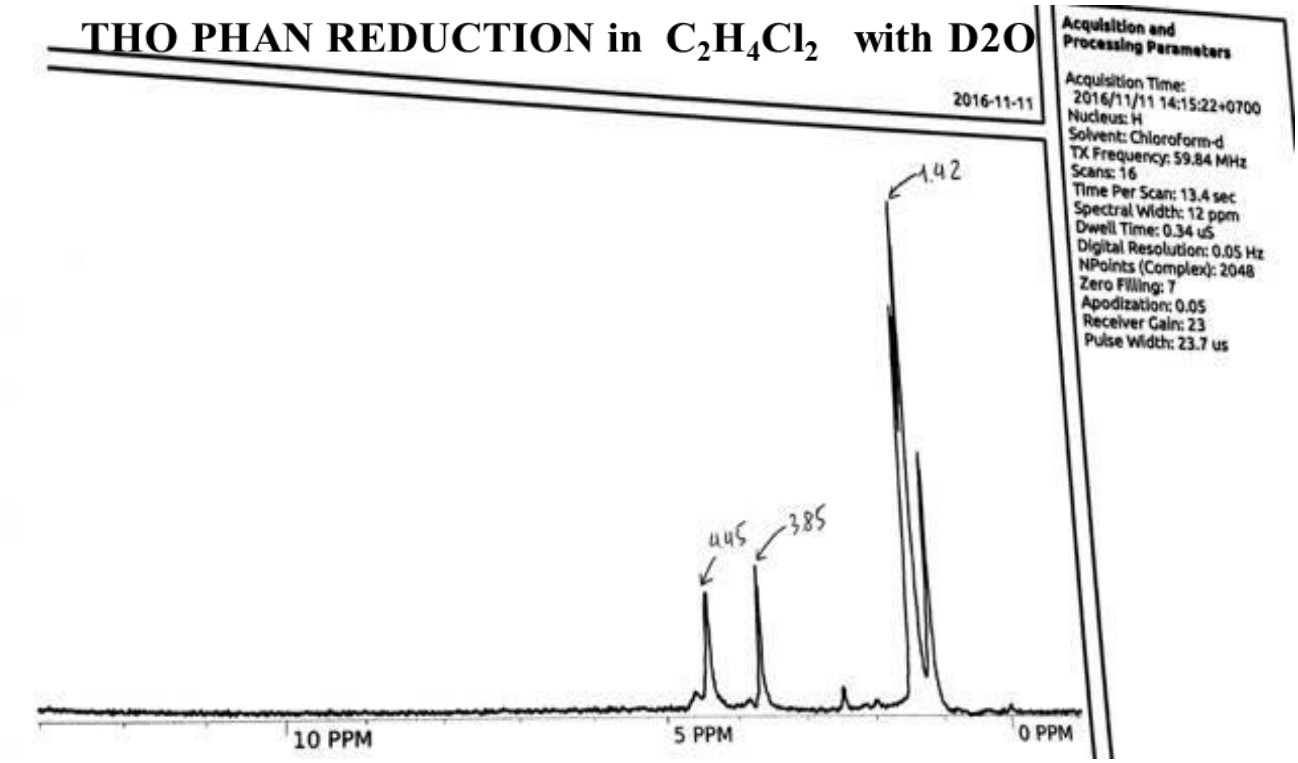
NMR peak at 9.62 ppm disappears, indicating it is NH, not aldehyde. As a results showed, we concluded that the EDC is not good reagent to synthesize amino aldehyde from amino acids.

✓ <u>With Pivaloyl Chloride:</u>

- The final product was dried out by Rotavap and characterized using NMR:



The some peaks of testing samples corresponding to the peaks of starting material compounds. But the peak of 10.15ppm is not sure that is aldehyde group or different group. Therefore, we tested with D20:



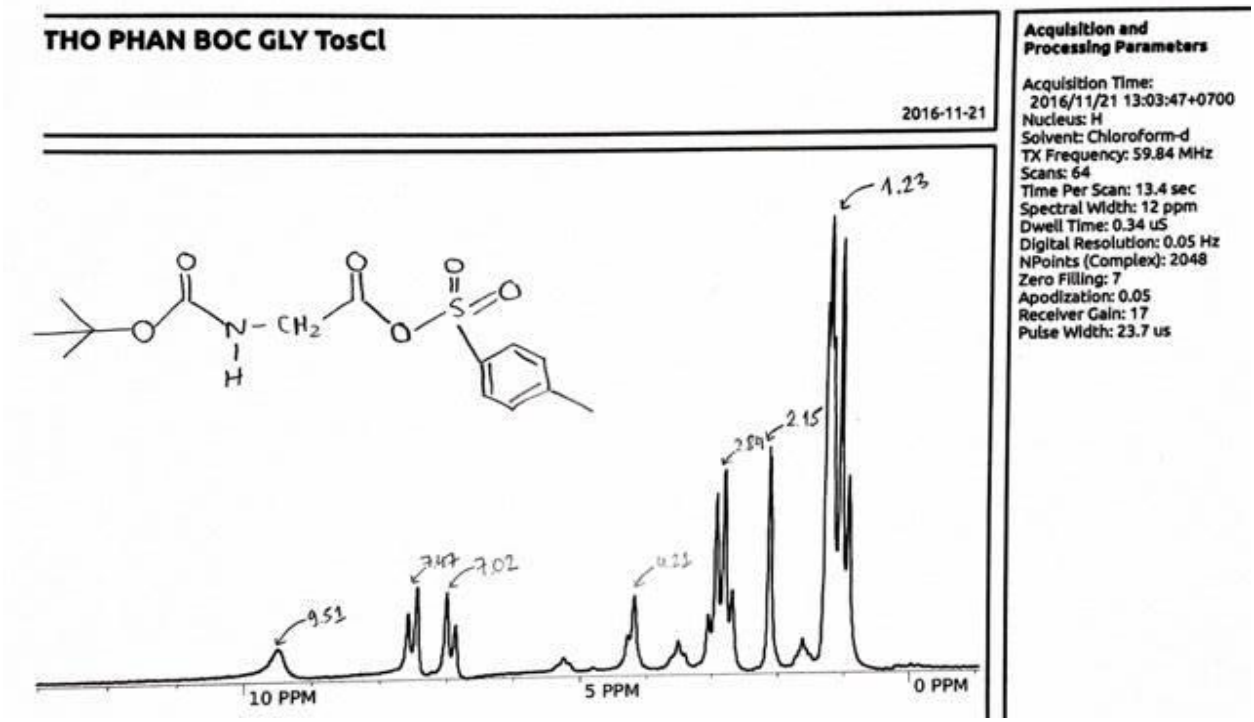
NMR peak at 10.15 ppm disappears, indicating it is NH, not aldehyde. NMR indicates that the aldehyde was not formed. Water workup converts the anhydride back to Boc Glycine. As a results showed, we concluded that the Pivaloyl Chloride is not good reagent to synthesize amino aldehyde from amino acids.

✓ **With Tosyl Chloride:**

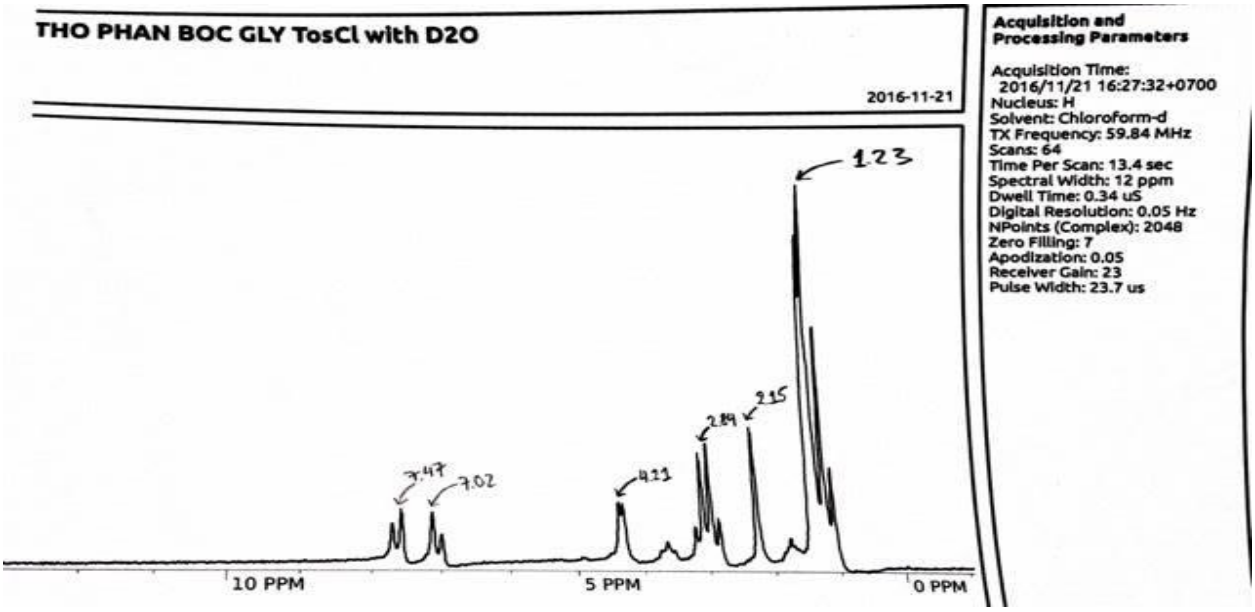
- After purified the crude product using flask chromatography, the TLC plates showed:

The color of the spots on the chromatogram of testing samples corresponding to that of starting material compounds. Therefore, we can be concluded that starting material is present.

- This product was dried out by Rotavap and characterized using NMR:

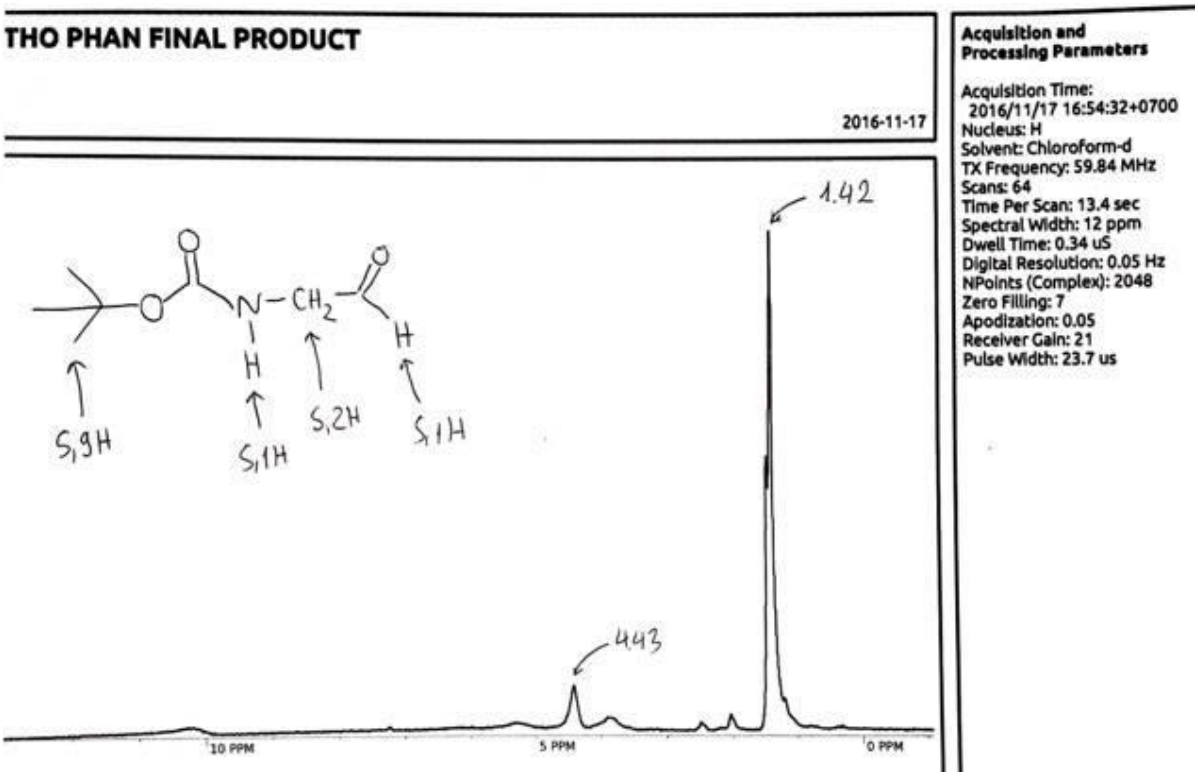


The some peaks of testing samples corresponding to the peaks of starting material compounds. But the peak of 9.51 ppm is not sure that is NH group or different group. Therefore, we tested with D20:



NMR peak at 9.51 ppm disappears, indicating it is not NH.

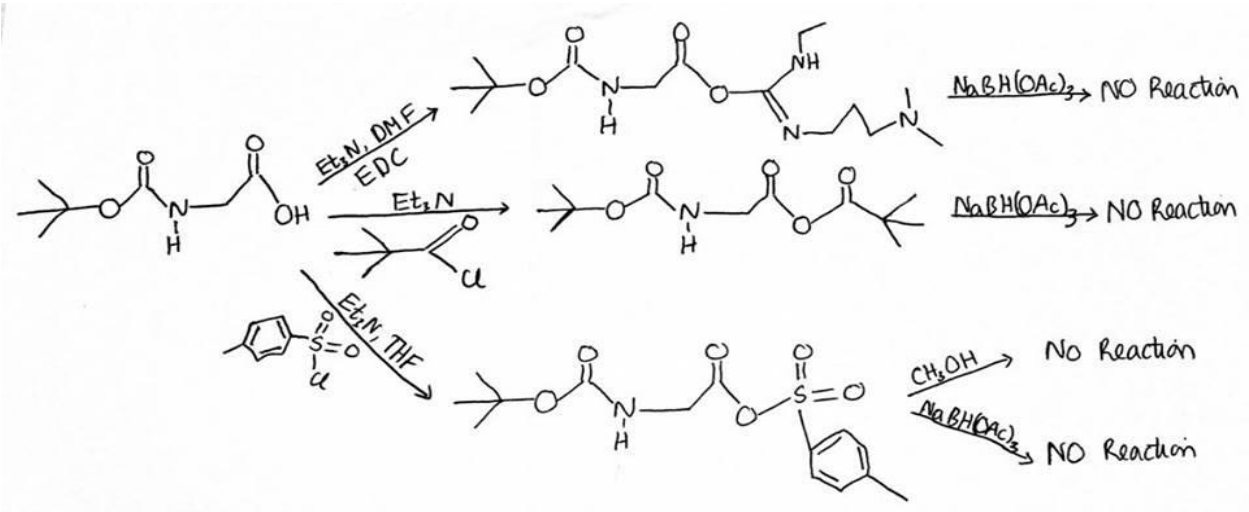
- The final product was dried out by Rotavap and characterized using NMR:



NMR does not clearly indicate the desired product has formed. As a results showed, we concluded that the Tosyl Chloride is not good reagent to synthesize amino aldehyde from amino acids.

CONCLUSION:

In summary, three methods were used to activate and reduce Boc Glycine. We were only successful in step 1 and step 2, but the final step is not successful:



Although, the conversion of Amino- aldehydes to Amino acids was not successful yet, I learned a lot of techniques and skills through in this project. I hope that in future experiments I will think about more activated reagents for the synthesis of Amino-aldehydes from Amino Acids.

Acknowledgments:

I would like to thank all of the people listed below. This project could not been done without your support.

- Dr. Phalguni Ghosh
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- Dr. Steven Rowley
- Dr. Parag Muley, Chair Person , Natural Sciences
- Dr. David Edwards, Dean, Natural Sciences
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- Bristol-Myers Squibb for financial support
- Chemistry Lab Staff : Douglas Reardon, David Rossen

Reference:

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