Synthesis and Characterization of Anagrelide Impurity

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Contents

Objective of the study.

- To obtain the particular impurity present in anagrelide.
- To study the characterization of that particular impurity.
- To get the maximum yield with unique procedure.

Company profile.

- It was established in **1991** and has a rich experience of over two and a half decades in the Pharmaceutical arena.
- The unit is Located in KSSIDC Industrial Estate, doddaballapur , Bangalore-561203
- Engaged in Contract Manufacturing and Manufacturing of APIs, Intermediates and Fine Chemicals,
- Recently got accreditation update as Quality Management System ISO 9001-2015 during the re-certification surveillance audit.

Introduction to Anagrelide.

- Anagrelide is a Heterocyclic aromatic compound with chemical formula $C_{10}H_7Cl_2N_3O$. It is a liquid with brown colour.
- Heterocyclic aromatic compounds play an important role in drug discovery and development and therefore tremendous efforts have been made to develop convenient and green synthesis routes for their high yielding synthesis.
- It appears to carry a better response rate than other thrombocythemia treatments (that is busulfan, hydroxyurea) and may be better responsive.[1]

- Anagrelide is a platelet-reducing agent used to lower dangerously elevated platelet levels (that is to treat thrombocythemia) in patients with myeloproliferative neoplasms. It is an oral imidazoquinazoline.
- It is an anti depressant, medicine to improve blood flow and prevent blood clots.

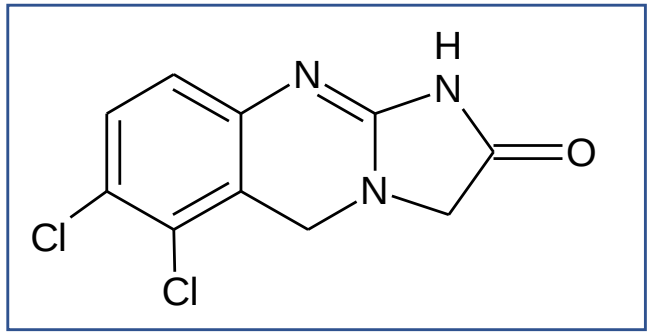


Fig 1:Anagrelide

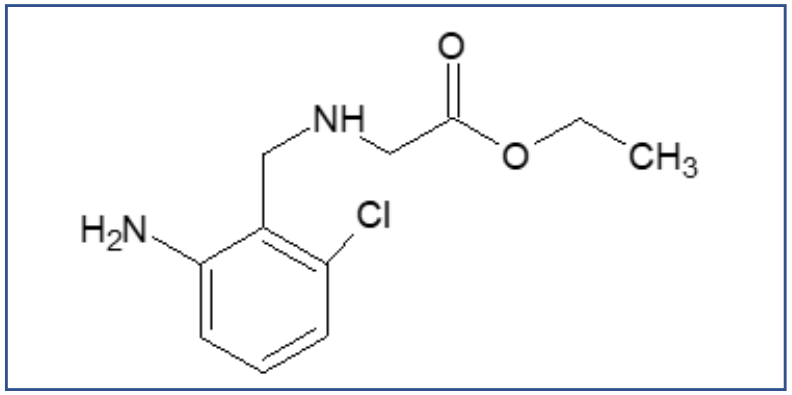


Fig 2: 6-amino 2-chloro glycine ethyl ester

Side Effects:

Some of the common side effects of anagrelide include headache, dizziness, fatigue, nausea, diarrhea, abdominal pain, constipation, loss of appetite, weight loss, heart palpitations, shortness of breath, chest pain, muscle pain or weakness, increased sweating, and insomnia. In rare cases, anagrelide may cause more serious side effects such as blood disorders, liver problems, heart failure, or severe allergic reactions.[2]

Applications:

- An antidepressant.
- A blood thinner or other medicine to treat or prevent blood clot.
- Anagrelide may impair female fertility. Female patients of reproductive age should be advised of the potential for adverse effects on fertility prior to initiating therapy.
- Anagrelide is used to decrease the number of platelets (a type of blood cell that is needed to control bleeding) in the blood of patients who have a bone marrow disorder.[3]

Literature Review

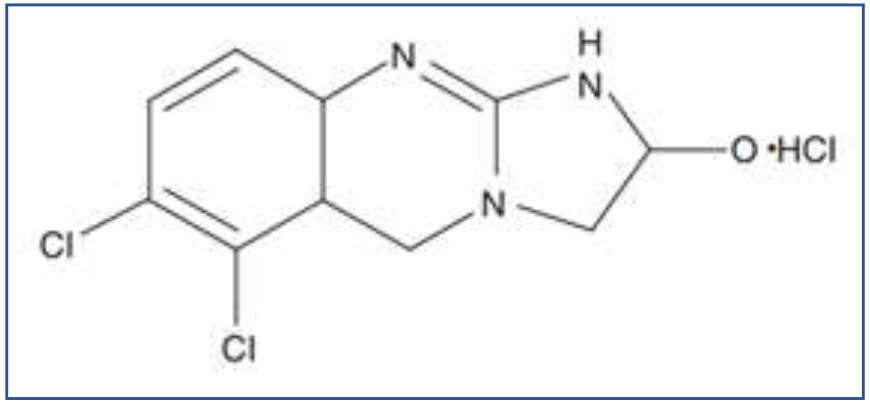


Figure 1: Structure of Anagrelide Hydrochloride

Carles Besses et al.,[4] has explained that Anagrelide hydrochloride (AG) is a derivative which reduces the high platelet count in Essential thrombocytemia (ET) patients. Initially the drug was investigated in vitro but it was later discovered in vivo conditions and little influence on platelet function but rapidly lowered platelet counts. Anagrelide is a selective and nonleukemogenic platelet reducing drug with proven efficacy in ET patients. In Europe, it is licensed as the second-line therapy for high-risk ET patients. Following oral administration of anagrelide in man, at least 70% is absorbed from the gastrointestinal tract. In fasted subjects, peak plasma levels occur about 1h after a 0.5 mg dose.

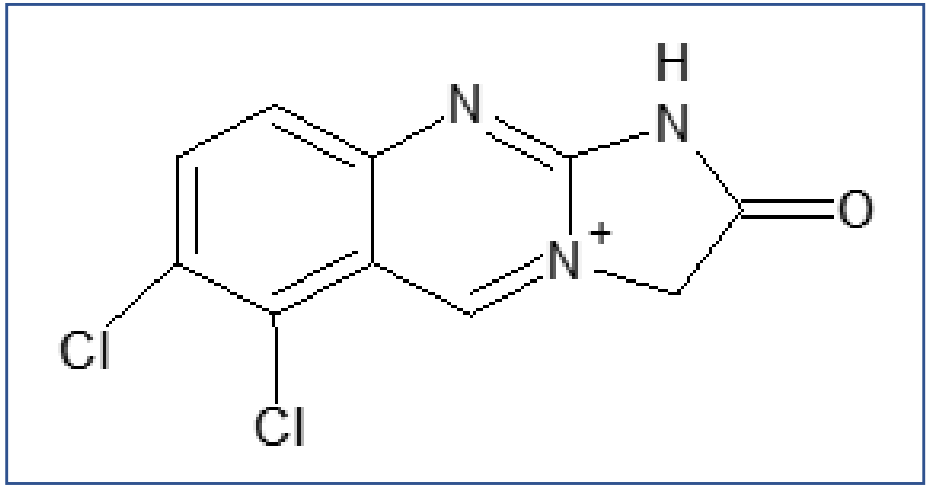


Figure 2: Structure of Anagrelide with Ketone

P. Trinka, et al., [5] explained about a simple and selective method for liquid chromatography, developed to determine the degradation impurities in solid oral dosage forms of Anagrelide (Antithrombocythemic agent).The infrared spectra were obtained using potassium bromide pellets using Bruker IFS- 113 spectrophotometer. The 'H NMR and 13C NMR measurements were performed using Bruker WM-250 instrument at 250 MHz ('H) and 62.89 MHz (13C), respectively, in DMSO-d6 solution using TMS and DDS, respectively, as internal standards, The validation studies demonstrated that the current HPLC method is reproducible, specific and accurate for its intended purpose. It is economically feasible and user-friendly method. The proposed method was successfully applied in quality control labs for stability analysis.

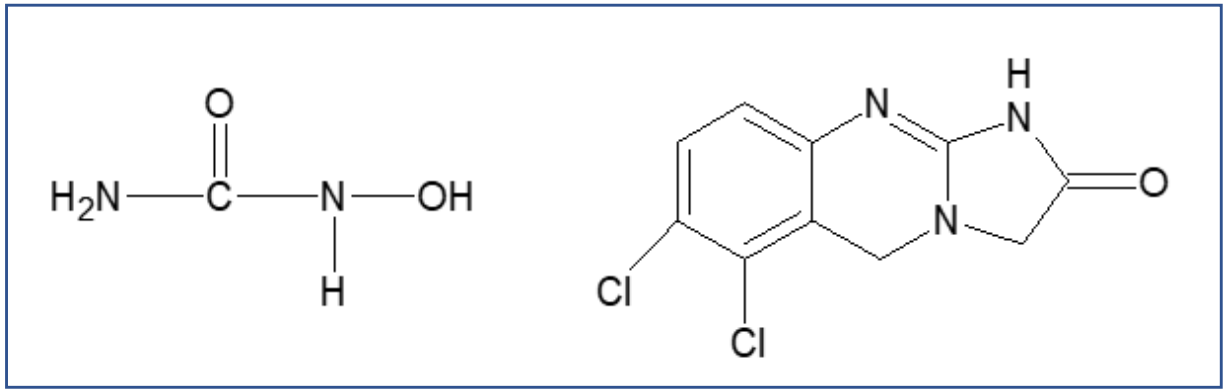


Figure 3: Structure of hydroxy urea and Anagrelide

Hong et al., [6] worked on anagrelide having different mechanisms of action, have been successfully used to reduce the platelet count in essential thrombocythemia and in thrombocythemia associated with other myeloproliferative disorders, particularly in polycythemias vera. Anagrelide is an imidazoquinazoline derivative that was initially developed as an inhibitor of platelet aggregation.35 Anagrelide is a potent inhibitor of a cyclic-AMP phosphodiesterase (Type III) found in platelets,43 and as a result raises cyclic-AMP levels in these cells.44 This action of anagrelide explains its inhibitory effect on platelet aggregation. In contrast, its main toxicity is cardiovascular, emanating from its vasodilatory and positive inotropic properties.

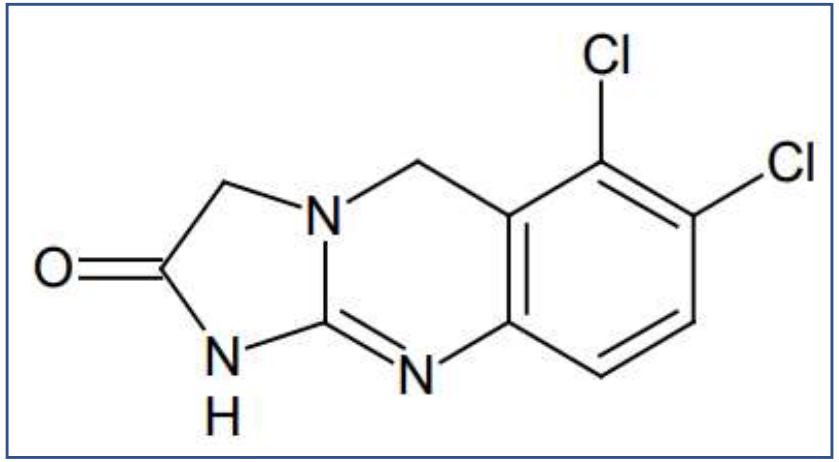


Figure 4: Structure of Anagrelide hydrochloride in Development and Validation of a Stability

Pujeri, et al.,[7] has developed a simple, rapid, and stability-indicating reverse-phase liquid chromatographic assay method was developed for Anagrelide Hydrochloride (ANG) in the presence of its degradation products generated from forced decomposition studies.

Pure ANG and its formulation AGRYLIN HPLC grade acetonitrile and methanol were purchased from Spectro hem, India. Potassium dihydrogen phosphate, hydrochloric acid, sodium hydroxide and hydrogen peroxide were obtained from Merck (Darmstadt, Germany). HPLC grade water obtained from a Milli-Q water purification system (Millipore, MA, USA) was used throughout the study. Preparation of Standard Solution: A stock solution of ANG (1.0 mg mL−1) was prepared by dissolving appropriate amount in the diluent. A standard solution of the drug was prepared by suitable dilution. To optimize the chromatographic conditions, the effect of composition of mobile phase, the flow rate and the detection wavelength were investigated. In this study, it was possible to develop a selective and validated stability-indicating HPLC assay method for Anagrelide hydrochloride on an ODS-3 column, which could separate the drug and its degradation products formed under a variety of stress conditions.

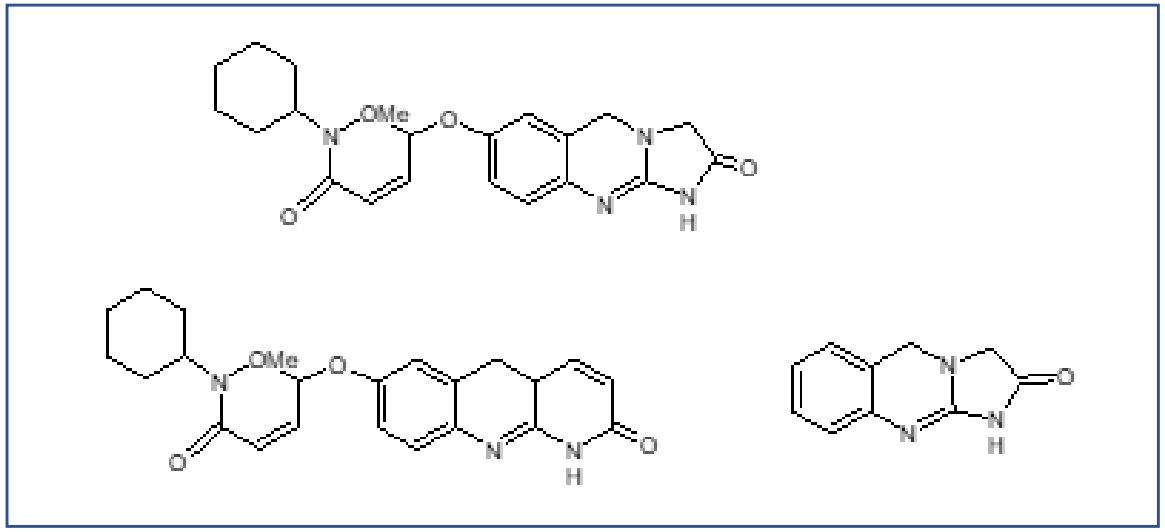
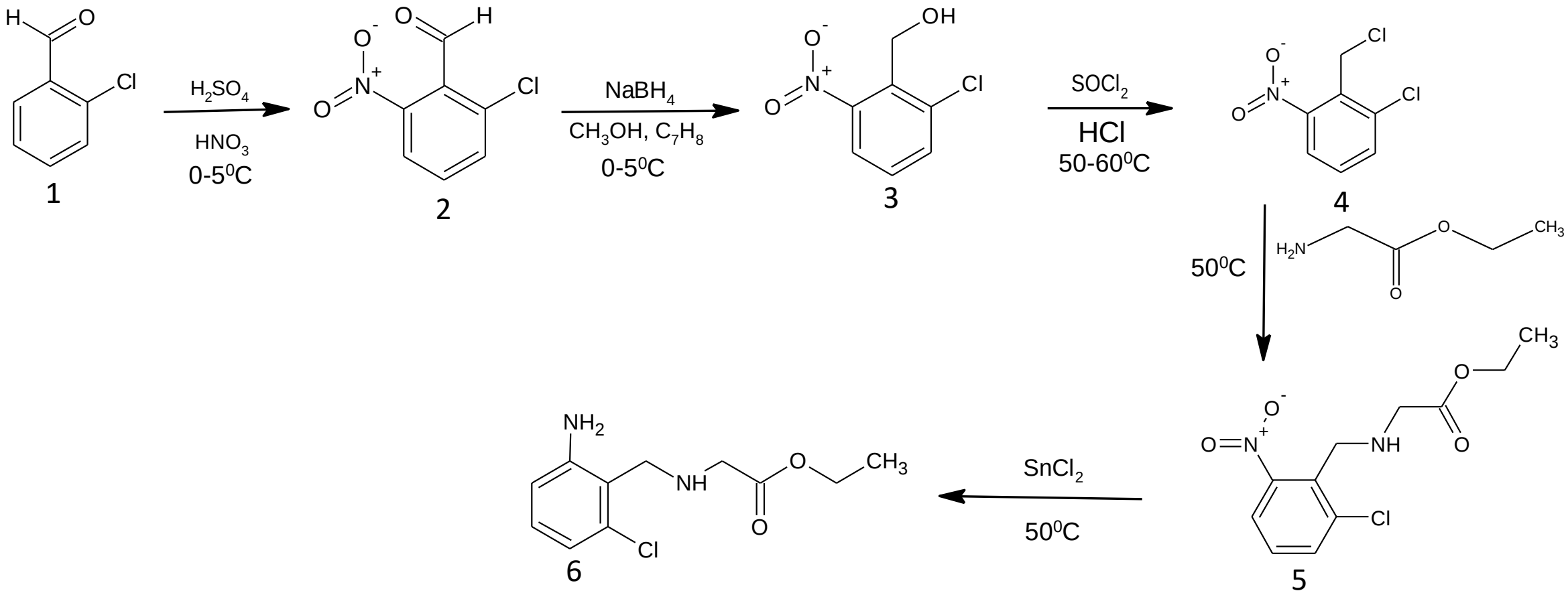


Figure 5: Inhibitors of Cyclic AMP Phosphodiesterase. Analogues of Cilostamide and Anagrelide.

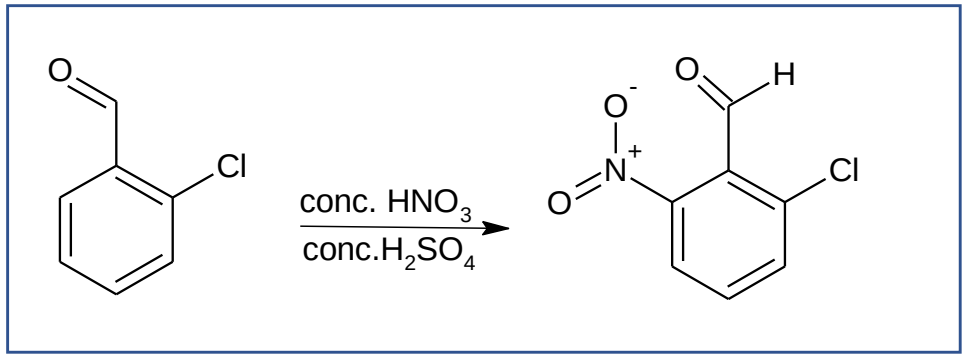
Jones, , et al.,[8] has proven the Evaluation of a series of lactam heterocyclic analogues of cilostamide as inhibitors of cyclic AMP phosphodiesterase derived from both human platelets and rat heart in comparison with their corresponding methoxy-substituted heterocycles has revealed that the N-cyclohexyl-N-methyl-4-oxybutyramide side chain of 2 is an important lipophilic and/or steric pharmacophore. Current therapeutic approaches to the treatment of heart failure rely on the stimulation of cardiac contractility with the administration of cardiac glycosides or sympathomimetic agents. The absence of a safe, orally active, positive inotropic agent has prompted the search for such drugs.

Experimental Section

Reaction Scheme: Preparation of 6-amino 2-chloro glycine ethyl ester.



Step 1:Preparation of 2-chloro 6-nitro benzaldehyde from ortho-chloro benzaldehyde.[9]



Raw materials:

Sl.No.	Chemicals used	Quantity	Mol. Wt.	Moles	Molar ratio
1	2-chloro Benzaldehyde	20.0 g	140g/mol	0.0142	1 eq
2	Conc. Nitric Acid	12.4 mL	63g/mol	0.019	1.461eq
3	Conc. Sulfuric Acid	147.2 mL	98g/mol	0.150	11.538
4	DM Water	500 mL	18.02g/mol	.....	25 V
5	Ethyl Acetate	200 mL	88.1g/mol	.....	10 V

Procedure:

- Three necked 250 ml round bottom flask was fixed to Overhead stirrer.
- Added conc. nitric acid (12.4ml) to the round bottom flask (RB) and charged 2-chloro Benzaldehyde (20.0g) at room temperature stirred for 10 minutes and the clear solution was obtained.
- Then charged with conc.sulfuric acid (147.2ml) drop wise at 0-5^{0}C temperature.
- It was stirred for 1 hour. Reaction mixture appeared to be white precipitate in the round bottom flask which indicates the completion of reaction. Then finally removed it from the ice bath. Completion of reaction was confirmed by TLC.

TLC Method:

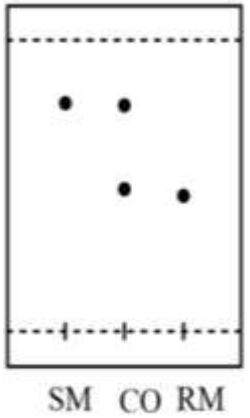
TLC Sample Preparation: 1mL of the reaction mixture was taken in a vial, starting material dissolved in ethyl acetate. Above samples spotted on TLC plate. TLC was run in ethyl acetate. The starting material was consumed completely in reaction mixture.

SM- starting material

CO- co spot (starting material + reaction mass)

RM-reaction mixture

Mobile phase**:** Ethyl acetate and Methanol in the ratio 9:1



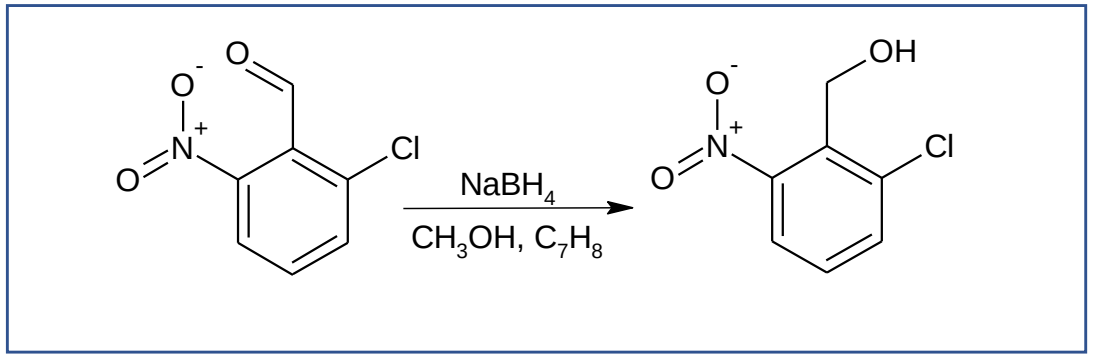
Work up:

- Quenched the reaction mass in ice cold demineralized water (500 ml).
- Stirred it for 10 mins.
- Extracted the reaction mass with ethyl acetate (200 ml).Then again extracted with (100 ml) ethyl acetate.
- Washed the ethyl acetate layer with demineralized water (200 ml).
- Dried ethyl acetate layer over anhydrous sodium sulphate and filtered it.
- Concentrated the ethyl acetate layer over vacuum rotavapor to get the solid.
- The reaction was observed through TLC. (If two spots occurred then it is refluxed with cyclohexane in round bottom flask (RB) and concentrated over rotavapor using cyclohexane layer).
- Then dried the product and weighed it. Completion of reaction was confirmed by TLC.

Result: The purity was good because TLC showed single spot. Theoretical M.P was 83˚C to 84˚C. Observed melting point was 82°C to 84°C.

- Theoretical yield: 15.32 g
- Experimental yield: 13.28 g
- Percentage of yield: 86.68

Step 2: Preparation of 2-chloro 6-nitrobenzyl alcohol from 2-chloro 6-nitro benzaldehyde.[10]



Raw materials:

Sl.No.	Chemicals used	Qty	Mol. wt.	Moles	Mole ratio
1	ortho-chloro 6-nitro benzaldehyde	13.28g	185.01	0.07177	1 eq
2	Sodium borohydride	3.30g	37.83	0.05733	1.1eq
3	Toluene	67.65 ml	92.14	0.1151	
4	Methanol	3.30 ml	32.04	…….	……..

Procedure:

- Three necked 250 ml round bottom flask (RB) was fixed to overhead stirrer.
- Then charged ortho chloro 6-nitro benzaldehyde (13.28g) and added toluene (67.65 ml), with maintained temperature of 0-5 ^{0}C with stirring.
- Charged with methanol stirred it for 10 minutes.
- Then charged sodium borohydride (3.30g) drop wise up to 20 minutes.

  After getting clear solution, Completion of reaction was confirmed by TLC.

TLC Method:

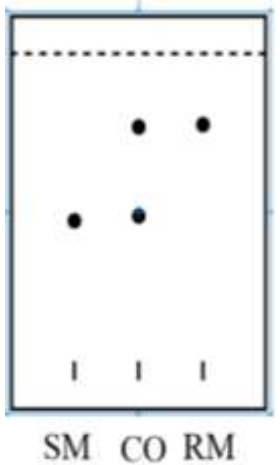
TLC Sample Preparation: 1mL of the reaction mixture was taken in a vial, starting material dissolved in ethyl acetate. Above samples spotted on TLC plate. TLC was run in ethyl acetate. The starting material was consumed completely in reaction mixture.

SM- starting material

CO- co spot (starting material + reaction mass)

RM-reaction mixture

Mobile phase**:** Ethyl acetate and Methanol in the ratio 9:1



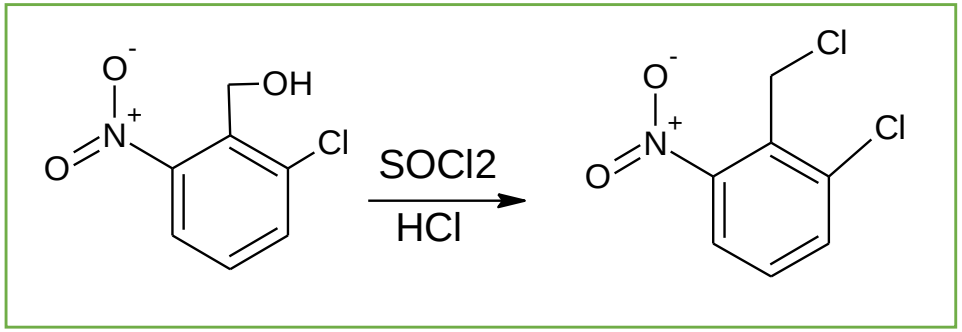
Work up:

- Added Demineralized water (30 ml) to that reaction mass.
- Stirred for 15 minutes at room temperature. (RT)
- Extracted toluene layer and aqueous layer using separating funnel. Then removed the aqueous layer.
- Washed toluene layer 3 times using DM water (25 ml).
- Dried toluene layer over anhydrous sodium sulphate and filtered it.
- Concentrated toluene layer using rotavapor pump and weighed the product.

Result: The purity was good because TLC showed single spot. Theoretical M.P was 135 ^{0}C. Observed M.P was 132^{0}C.

- The theoretical yield: 13.06 g
- The experimental yield: 12.9 g
- Percentage yield: 98.77

Step 3: Preparation of 2-chloro 6-nitrobenzyl chloride from 2-chloro 6-nitrobenzyl alcohol.[11]



Raw materials:

SL No	Chemicals used	Qty	Mol. wt.	Moles	Mole ratio
1	ortho-chloro 6-nitro benzyl alcohol	12.9g	187g/mol	0.0745	1 eq
2	Tri Ethyl Amine	4.455g	101.19g/mol	0.0440	1.7 eq
3	Thionyl Chloride	5.8ml	118.97g/mol	0.0245	2.3eq
4	Toluene	56.30ml	92.14g/mol	…..	……

Procedure:

- Three necked 250ml round bottom flask (RB) was fixed to overhead stirrer.
- Charged the Ortho chloro 6-nitro benzyl alcohol (12.9g) added with toluene (56.30ml) just to dissolve product and added tri ethyl amine (TEA), about (4.455g). Maintained temperature 0-5^{0}C.
- Stirred it until solution temperature becomes stable for above condition.
- Charged thionyl chloride ($SOCl_2$) slowly for about 15 mins.
- Stirred it for 2 hours in water bath at 50-60^{0}C. Completion of reaction was confirmed by TLC.

TLC method :

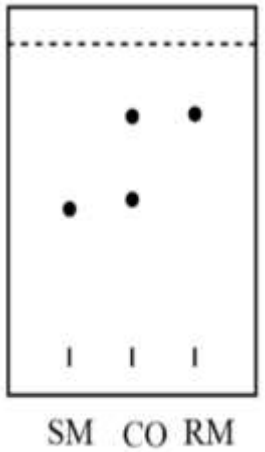
TLC Sample Preparation: 1mL of the reaction mixture was taken in a vial, starting material dissolved in ethyl acetate. Above samples spotted on TLC plate. TLC was run in ethyl acetate. The starting material was consumed completely in reaction mixture.

SM- starting material

CO- co spot

RM-reaction mixture

Mobile phase**:** Ethyl acetate and Methanol in the ratio 9:1



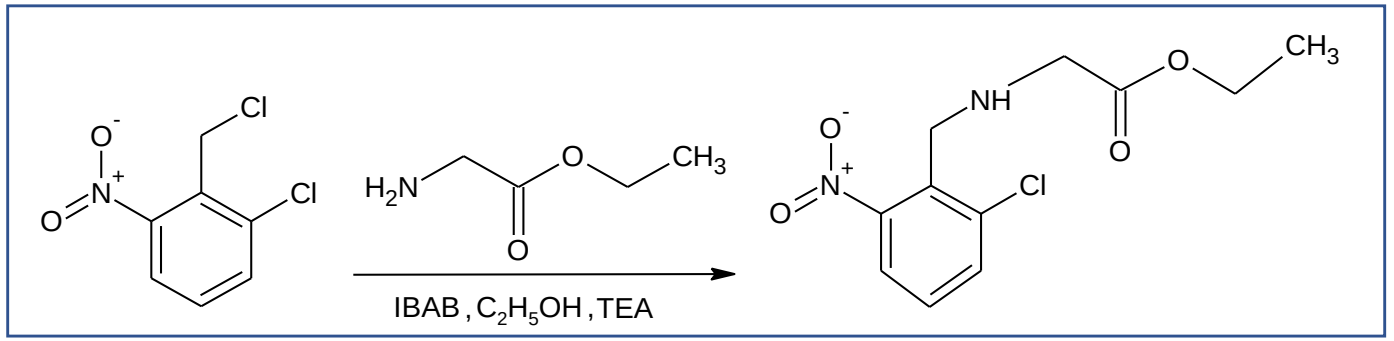
Work up:

- Product was washed with demineralized water (DM) for three time, each time with (60 ml).
- Separated the toluene layer and aqueous layer, removed the aqueous layer.
- Dried the toluene layer with anhydrous sodium sulphate solution.
- Filtered sodium sulphate using cotton.
- Concentrated the toluene layer over rotatory vapor vacuum pump.
- Dried the product and weighed the product.

Result: The purity was good because TLC showed singles spot. Theoretical M.P was 137.9^0C-141^0C. Observed M.P was 136^0C-140.3^0C.

- The theoretical yield: 13.06 g
- The experimental yield: 12.9 g
- Percentage yield: 98.77

Step 4: Preparation of 2-chloro 6-nitrobenzylethyl glycine from 2-chloro 6-nitrobenzyl chloride.[12]



Raw materials:

SL No.	Chemicals used	Qty	Mol. Wt.	Moles	Mole ratio
1	Ortho-chloro 6-nitro benzyl chloride	10.1 g	205	0.049g/mol	0.1eq
2	Ethyl glycine	25g	139.58	0.1791g/mol	2eq
3	IBAB	0.2g	……	----	---
4	Ethanol	10ml	……	.....	.....
5	Tri Ethyl amine	22.94g	101.19	0.2267g/mol	

Procedure:

- Three necked 250 ml round bottom flask (RB) was fixed to overhead stirrer.
- Then charged ortho chloro 6-nitro benzyl chloride (10.1g) ethyl glycine, IBAB catalytic quantity (0.2g) and tri ethyl amine (22.94 g). kept it for stirring in water bath at 50 ^{0}C about 9 hours. Completion of reaction was confirmed by TLC

TLC Method:

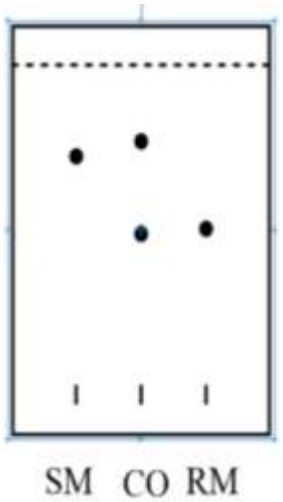
TLC Sample Preparation: 1mL of the reaction mixture was taken in a vial, starting material dissolved in ethyl acetate. Above samples spotted on TLC plate. TLC was run in ethyl acetate. The starting material was consumed completely in reaction mixture.

SM- starting material

CO- co spot (starting material + reaction mass)

RM-reaction mixture

Mobile phase**:** Ethyl acetate and Methanol in the ratio 9:1.



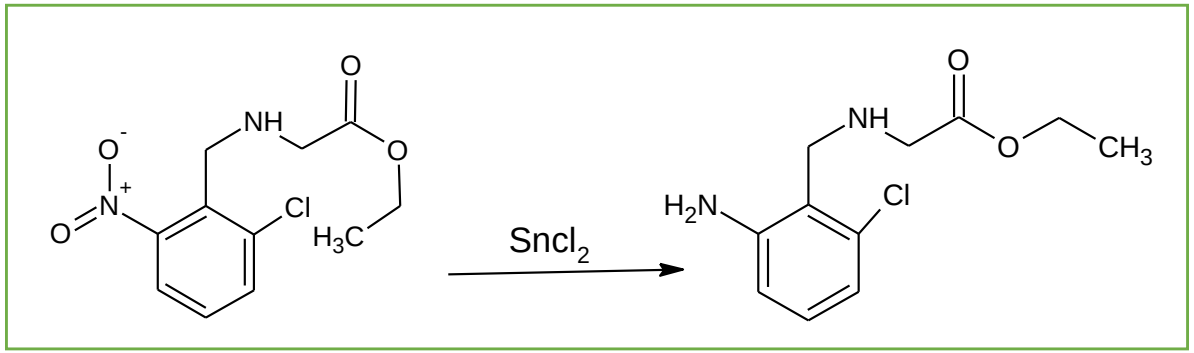
Work up:

- Transferred reaction mixture (RM) to single neck round bottom (RB) flask and concentrated the ortho chloro 6-nitro benzyl chloride solution over rotatory vapour vacuum pump.
- Charged demineralized water (60 ml), stirred for half an hour.
- Filtered the aqueous layer, charged solid product to beaker, and added dichloromethane (100 ml) and then stirred.
- Dried the reaction mixture (RM) over anhydrous sodium sulphate and filtered through cotton.
- Took round bottom flask (RB) and charged the above solution, then added Charcoal.
- Stirred for 15 minutes at room temperature and refluxed it for 30 minutes and filtered.
- To the filtrate added n-hexane (10 ml). and concentrated the above reaction mixture (RM).
- Charged 20 ml n-hexane, cooled it to temperature about 0-5 ^{0}C.
- Filtered the precipitate. Dried the product and weighed it.

Result: The purity was good because TLC showed single spot. Theoretical M.P was 137.9 - 141^0 C. Observed M.P was 130^{0}C.

- The theoretical yield: 7.62 g
- The experimental yield: 7.11 g
- Percentage yield: 93.30

Step 5: Preparation of 6-amino 2-chloro glycine ethyl ester from2-chloro 6-nitrobenzylethyl glycine.[13]



Raw materials:

Sl no	Chemicals used	Qty	Mol. Wt.	Moles	Mole ratio
1	ortho-chloro 6-nitro benzyl ethyl glycine	10.11	272g/mol	0.0371	0.1eq
2	Stannous chloride	13.5g	139.58g/mol	0.1791	0.2eq
3	Con. HCl	27ml	36.46g/mol	……..	…….
4	IPA-HCL	10 ml	110.57g/mol	……	……..

Procedure:

- Three necked 250 ml round bottom flask (RB) was fixed to overhead stirrer.
- Then charged product and added conc. HCL (27ml), Maintained temperature to 0-5 ^{0}C.
- Took separate boiling tube. Charged stannous chloride (13.5g) and added conc. HCL until it dissolves.
- After reaction mixture attaining 0-5 ^{0}C started adding stannous chloride solution for about 30 minutes with maintaining temperature 0-5 ^{0}C.
- After 30 minutes stirred it at 50 ^{0}C about one hour (until become clear solution). Completion of reaction was confirmed by TLC

TLC Method:

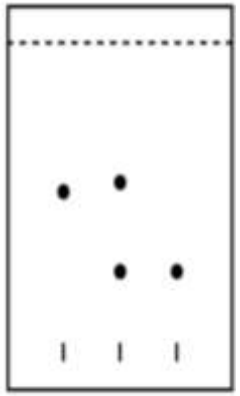
TLC Sample Preparation: 1mL of the reaction mixture was taken in a vial, starting material dissolved in ethyl acetate. Above samples spotted on TLC plate. TLC was run in ethyl acetate. The starting material was consumed completely in reaction mixture.

SM- starting material

CO- co spot (starting material + reaction mass)

RM-reaction mixture

Mobile phase**:** Ethyl acetate and Methanol in the ratio 9:1



Work UP:

- Cooled the RM at 0-5^{0}C about one hour.
- Filtered the solution.
- Dried the product.
- Weighed the product.

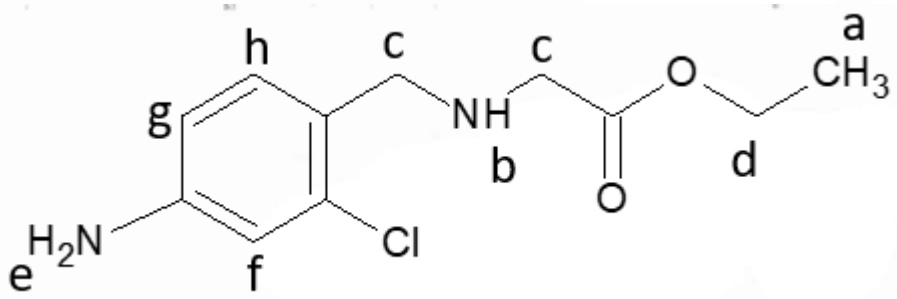
Result: The purity was good because TLC showed single spot. Theoretical M.P was 137.9-141^{0}C. Observed M.P was 130^{0}C.

- The theoretical yield:11.36 g
- The experimental yield: 10.70 g
- Percentage yield: 94.19

Analytical data:

^{1}HNMR Spectroscopy of 6-amino 2-chloro ethyl glycine.

$_{1}H^{1}$ Proton	Chemical Shift values (ppm)
a	1.213 (3H,t)
b	3.007 (1H, s)
c,c	3.1 (4H, s)
d	3.34 (2H,q)
e	4.09 (2H, dd)
f	6.70 (1H, s)
g	6.44 (1H d): J=8.5 Hz
h	6.99 (1H d): J=2.7 Hz

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Reviewed by       = Ramesh
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Results And Discussion

Compounds	Theoretical M.P	Observed M.P	Theoretical yield	Observed yield	Percentage yield
2-chloro 6-nitrobenzaldehyde	83°C-84°C	84°C-86°C	15.32 g	13.28 g	86.68
2-chloro 6-nitrobenzyl alcohol	135^0C-137^0C	132^0C-134^0C	13.06 g	12.9 g	98.77
2-chloro 6-nitrobenzyl chloride	137.9^0C-141^0C	136^0C-140.3^0C	11.76 g	10.1 g	85.88
2-chloro 6-nitrobenzyl ethyl glycine	137.9^0C - 141^0C	131.4 ^{0}C-139.1^0C	7.62 g	7.11 g	93.30
6-amino 2-chloro glycine ethyl ester	137.9^0C-141^0C	130^0C-135.5^0C	11.36 g	10.70 g	94.19

Conclusion

During this project prepared Anagrelide impurity i.e., 6-amino 2-chloro glycine ethyl ester with a concise procedure included with 5 step reactions.

Also learnt about the lab techniques such as literature search, planning of reaction, execution of reaction, isolation of procedure such as (TLC) and characterization of the organic compounds using ^{1}HNMR and IR spectroscopy. Along with the lab technique, learned and practiced EHS (Environmental Health and safety) policy. Safe Handling of Chemicals, personal and work place safety, disposal of used chemicals, and learned to work in lab as a team.

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Thank
You!