Nature of Invention: Chemical molecule and synthesis route

Applicant: National Chemicals Limited [NCL]

Inventors: Rohan Nimesh, Piyush Kumar, Prakhar Nanda

Chemical Formula: $C_{13}H_{18}Br_2N_2O$

Chemical Name: trans-4-(2-Amino-3,5-dibromobenzylamino)-cyclohexanol

Chemical synthesis routes:

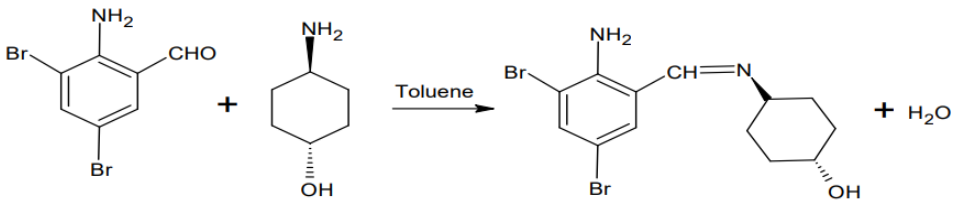
PREPARATION OF AMBROXOL USING TOLUENE

Raw materials used:

- 2-Amino-3, 5-dibromo benzaldehyde
- Trans-4-Aminocyclohexanol
- Toluene
- Sodium Borohydride
- Methanol
- Charcoal

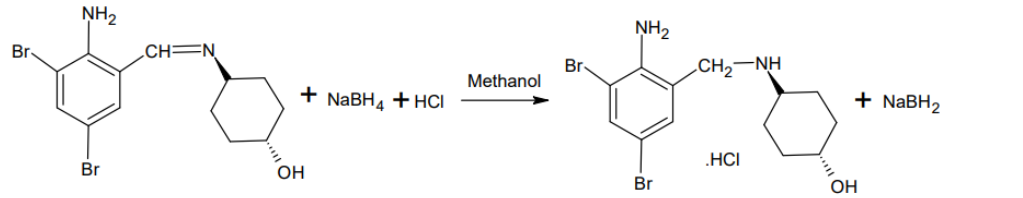
Reactions involved:

Step-I: Preparation of Stage-I Intermediate



ADBA		TACH		Stagel Intermediate		Water
$C_7H_5NOBr_2$	+	$C_6H_{13}NO$	=	$C_{13}H_{16}N_2OBr_2$	+	H_2O
MW: 279	+	115		376	+	18
Total:	394			394		

Step-II: Preparation of Ambroxol Hydrochloride



Stagel Intermediate		Sodium borohydride	HCl		Ambroxol.HCl		Inorganic Borate salt
$C_{13}H_{16}N_2OBr_2$		+ $NaBH_4$	+ HCl		$C_{13}H_{19}N_2OBr_2Cl$	+	$NaBH_2$
MW: 376		+ 38	+ 36.5		414.5	+	36
Total:	450.5				450.5		

Operational steps:

- **Condensation:**
  2-amino-3,5-dibromo benzaldehyde and Trans-4-Aminocyclohexanol
  stir in a solvent, and the temperature control reaction gets Schiff bases solution.
- **Reduction:**
  The Schiff bases solution temperature control with step a obtains, add sodium borohydride or lithium aluminium hydride (we are using sodium borohydride) under the agitation condition, the temperature control reaction gets the Trans broncho alkaline solution.
- **Salify:**
  With the Trans broncho alkaline solution cooling that step b obtains, regulate pH value with the hydrochloric acid solution under the agitation condition, the temperature control reaction is filtered, and washes and drying gets Ambroxol HCl.

The yield of the step-1 reaction is 90.16%
The yield of the step-2 reaction is 71.17%
*The final purity is 83***%**

Additional information (procedure and reaction conditions):

- Above-mentioned preparation method, 2-amino-3 among the step a, the mol ratio of 5-dibromo benzaldehyde and trans-4-amino cyclohexane is 1:1-2, preferred 1:1.2; Temperature of reaction is 40 ℃-solvent boiling point temperature, preferred 60 ℃-65 ℃; Reaction times is 3-8h.

- Above-mentioned preparation method, the sodium borohydride that is added among the step b or the molar weight of lithium aluminum hydride is the 2-amino-3 among the step a, 5-dibromo benzaldehyde 1.1-1.5 times, and preferred 1.2 times; Temperature of reaction is 0 ℃-40 ℃, preferred 20 ℃-30 ℃; Reaction times is 6 hr. Preferred 20 ℃-30 ℃ of temperature can make the reaction's temperature fast herein. The temperature-low reaction is slower, not exclusively; the high-temperature reaction is violent and can produce more impurities.

- In the above-mentioned preparation method, the Trans broncho alkaline solution is cooled to 10 ℃-20 ℃ in step c.

- The Above-mentioned preparation method, regulating the pH value among step c, is 1-4, preferred 2-3. When the pH value was 2-3, the products obtained therefrom were white, and the yield was higher. the pH value was too low, the production color was partially yellow, and the high product yield was on the low side for the pH value.

- Above-mentioned preparation method, the temperature of step c reaction is 0 ℃-20 ℃, preferred 0 ℃-5 ℃, and the time of reaction is 2-6 hr. The product yield was higher when the reaction temperature was 0 ℃-5 ℃.

PREPARATION OF AMBROXOL USING METHYL ANTHRANILATE

The method takes methyl anthranilate as a starting material, has simple reaction steps, can finish ambroxol hydrochloride by only three steps, and has high reaction yield and high purity.

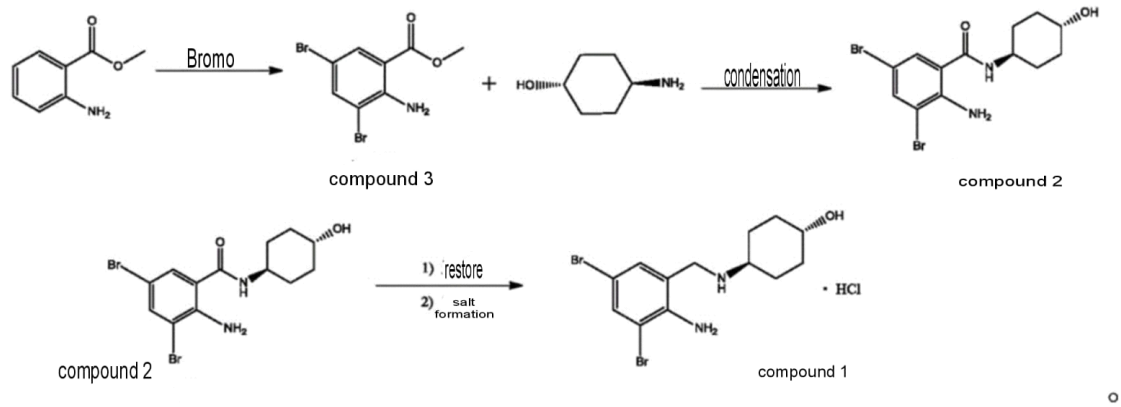
Operational steps:

- Carrying out bromination reaction on methyl anthranilate to generate a compound
- Carrying out ester amine condensation on the compound 3 and trans-4-aminocyclohexanol to generate a compound 2.
- Reducing the compound 2 by carbonyl group, and salifying to obtain ambroxol hydrochloride.

->The carbonyl reducing agent is hanster 1, 4-dihydropyridine, the catalyst is trifluoromethanesulfonic anhydride, and the mixture is stirred at room temperature for reaction.

-> The salifying step is as follows: dissolving with acetone, dropwise adding concentrated hydrochloric acid under stirring at room temperature to obtain light yellow precipitate, stirring at room temperature, filtering, washing with acetone to obtain light yellow crude product, recrystallizing with water, decolorizing with activated carbon, and drying to obtain white ambroxol hydrochloride.

Reactions involved:



Additional information (procedure and reaction conditions):

Step 1: The brominating agent is molecular bromine, the mass fraction is 30%, and the oxidant is hydrogen peroxide; the mass ratio of methyl anthranilate to molecular bromine is 1: 1.0-1.4; the reaction solvent is dichloromethane and water, the volume ratio of the dichloromethane to the water is 2:1, and the volume ratio of the hydrogen peroxide to the dichloromethane is 1: 10. Wherein the mass ratio of methyl anthranilate to molecular bromine is 1: 1.1.

Step 2: The reaction time is 1-3 hours at room temperature. Wherein, the reaction solvent is N, N-dimethylformamide; the reaction molar ratio of the compound 3, the trans-4-aminocyclohexanol, the DIC and the organic base is 1:1.2:0.4:1.5, and the weight ratio of the compound 3 to the DMAP substance is 1: 0.10.

Step 3: The mass ratio of the compound 2, the trifluoromethanesulfonic anhydride and the hanster 1, 4-dihydropyridine is 1: 0.05-0.2: 1-2. Wherein the mass ratio of the compound 2, the trifluoromethanesulfonic anhydride and the hanster 1, 4-dihydropyridine is 1: 0.08-0.12: 1-1.5, and more preferably, the mass ratio of the compound 2, the trifluoromethanesulfonic anhydride and the hanster 1, 4-dihydropyridine is 1:0.1: 1.2.

Synthesis of Compound 3

- 30mmol of methyl anthranilate was weighed into a three-necked flask, and 60mL of methylene chloride and 42mL of water were added thereto and sufficiently stirred.
- 60mL of dichloromethane are added into the constant pressure funnel, 33mmol of molecular bromine is accurately weighed and added into the constant pressure funnel, and a dichloromethane solution of bromine is slowly dropped.
- And (3) slowly dropwise adding 12mL of uniformly mixed solution of 30% hydrogen peroxide and 18mL of water in mass fraction into the reaction system while dropwise adding molecular bromine, fully stirring, and tracking the reaction process by TLC.
- After the reaction was completed, water was added to the system until the solid was completely dissolved, followed by liquid separation and washing of the aqueous phase with dichloromethane until colorless and transparent.
- An appropriate amount of sodium bicarbonate solid and 50mL of dichloromethane were slowly added to the aqueous phase, stirred well, and extracted to obtain an organic phase.
- The crude product was recrystallized from ethanol/water to give 8.985g of solid in **96.86% yield and 99.92% purity.**

Synthesis of Compound 2

- Suspending 20mmol of compound 3, 24mmol of trans-4-aminocyclohexanol, 8mmol of DIC and 2mmol of DMAP in a reaction bottle containing 100mL of N, N-dimethylformamide.
- dropwise adding a mixed solution of 30mmol of pyridine and 50mL of N, N-dimethylformamide under the stirring of ice water bath, continuing stirring for 1 hour after dropwise adding is finished within 20 minutes, and then heating to room temperature and stirring for 2 hours.
- Stopping stirring, adding the reaction solution into water for pulping, performing ice-bath crystallization, filtering, and drying under reduced pressure to obtain 4.222g of compound 2 as a solid, **wherein the yield is 96.14%, and the purity is 99.86%.**

Synthesis of ambroxol hydrochloride:

- Adding 10mmol of compound 2 and 1mmol of trifluoromethanesulfonic anhydride into a round-bottom flask in sequence, dissolving in 50mL of toluene, stirring for 0.5h
- adding 12mmol of hans-ester 1, 4-dihydropyridine, stirring at room temperature for reaction for 1h, adding 20mL of water, separating out an organic phase, washing with water, washing with saturated salt water, drying the organic phase, concentrating under reduced pressure
- adding 100mL of acetone for dissolution, dropwise adding 5mL of concentrated hydrochloric acid while stirring at room temperature to generate a light yellow precipitate, stirring at room temperature for 1h, filtering, and washing with acetone to obtain a light yellow crude product.
- Recrystallizing with water, decolorizing with activated carbon, and drying to obtain 2.345g of ambroxol hydrochloride with **yield of 96.85% and purity of 99.84%.**

References:

- https://patents.google.com/patent/CN103012167A/en (TOLUENE)
- https://patents.google.com/patent/CN111072499A/en (METHYL ANTHRANILATE)
- Aarkamedicare (Kolkata) official document https://environmentclearance.nic.in/DownloadPfdFile.aspx?FileName=BSw1gtt2gWR2X5TPDa/rWHYsD04Hxo/lWT9yd7mkjKDyzHvyvpJtnKGLxQTFiaMfjzH4HaHi9m1SHnSKXXiACIMxEFyzv/n2LxdjbCqHsHcJlHkeJX320CVWQWqwy+7n&FilePath=93ZZBm8LWEXfg+HAlQix2fE2t8z/pgnoBhDlYdZCxzXmG8GlihX6H9UP1HygCn3pCkAF2zPFXFQNqA4krKa1Aw==
- Some other company's official document (source was not found)

https://environmentclearance.nic.in/DownloadPfdFile.aspx?FileName=X2q+XZTe48d8LmPYRiMZ57XOK4qeM79ScXmoMvRlGIF0DoWHf8ygJlm/j5ymdcMGVszh1F3maHUA2r+g98s+jP0iTZOuWa07KMgeW0oLY9C0RUeS7+HNlrivhjLcLTlN&FilePath=93ZZBm8LWEXfg+HAlQix2fE2t8z/pgnoBhDlYdZCxzXTbTpOQqzWjBW0IF63rxBVcDlG0LKdfbGNs0Ou/TEvAA==

- For a Simple and efficient ambroxol synthesis method https://patents.google.com/patent/CN102351720B/en
- New insights into bromination process: effective preparation of Ambroxol | Chemical Papers (springer.com)

List the contributions of each author:

- Rohan Nimesh came up with the process and yield calculation that we will be using to manufacture ambroxol in our company.
- Prakhar Nanda came up with another method of producing Ambroxol Hydrogen Chloride with better yield and purity (using Methyl Anthralinate) along with the coordination of Piyush Kumar, although the yield and purity of the chemical is more the scalability of the innovation is yet to be discussed thus not used in our company for manufacturing purposes for the time being.

Name	Roll No	Signature
CEO - Sidhant Thalor	221055	Sidhant
First author - Rohan Nimesh	220907	Rohan
Second Author - Piyush Kumar	220766	Piyush
Third Author - Prakhar Nanda	220784	Prakhar

Nature of Invention: Chemical molecule and synthesis route

Applicant: National Chemicals Limited [NCL]

Inventors: Roshan Patil

Chemical Formula: $C_5H_8O_2$

Chemical Name: Acetylacetone

Chemical synthesis routes:

Preparation of Acetylacetone using Claisen Reaction

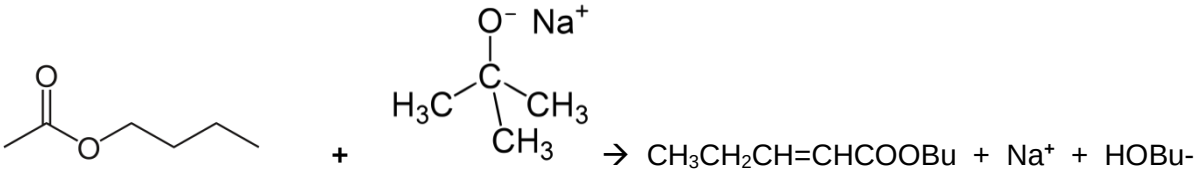
Raw materials used:

- Acetone
- Butyl acetate
- Sodium butoxide (NaOBu)
- Inert solvent (e.g., n-heptane)
- Distillation apparatus

Reactions involved:

Step I: Enolate formation (pre-condensation):-

NaOBu (strong base) deprotonates butyl acetate to generate an enolate ion:

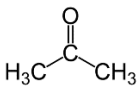


$CH_3CH_2CH_2CH_2COOBu + NaOBu \rightarrow CH_3CH_2CH{=}CHCOOBu + Na^+ + HOBu^-$

(Butyl acetate) (Sodium butoxide) (Enolate ion)

Step II : Claisen Condensation:-

The enolate ion acts as a nucleophile and attacks the carbonyl carbon of acetone:



$CH_3CH_2CH{=}CHCOOBu + CH_3C{=}O \rightarrow CH_3C(CH_3){=}CH\text{-}CH(COOBu)_2$

(Enolate ion) (Acetone) (Intermediate)

Step III: Deprotonation and product formation:-

Another molecule of sodium butoxide deprotonates the intermediate, leading to the final product (sodium acetylacetonate):

$CH_3C(CH_3)=CH-CH(COOBu)_2$ + NaOBu → $CH_3C(CH_3)=CH-COCH_3$ + Na+ + BuOH
(Intermediate) (Sodium butoxide) (Sodium acetylacetonate) (Butanol)

Step IV: Acidification and extraction (workup):-

The reaction mixture is acidified with hydrochloric acid to liberate acetylacetone from sodium acetylacetonate:

$CH_3C(CH_3)=CH-COCH_3$ + HCl → $CH_3C(CH_3)=CH-COCH_3$ + NaCl

(Sodium acetylacetonate) (Hydrochloric acid) (Acetylacetone) (Sodium chloride)

Acetylacetone is then extracted using an organic solvent like dichloromethane for purification.

Overall Yield of the Reaction: 83.6%
Final Purity: 78%

Operational steps:

- Dissolve sodium butoxide in an inert solvent to form a homogenous solution.
- Add butyl acetate to the solution slowly while stirring constantly.
- Maintain a cool temperature (around 10°C) during this addition.
- Once all the butyl acetate is added, slowly add acetone while maintaining the temperature below 40°C.
- After adding all the acetone, increase the reaction temperature to 80-85°C and maintain it for several hours (typically 3 hours).
- Allow the reaction mixture to cool down to room temperature.
- The product (sodium acetylacetonate) will precipitate as crystals. Separate the crystals from the solvent by filtration.
- Acidify the filtrate with a dilute acid (e.g., hydrochloric acid) to liberate acetylacetone.
- Extract the acetylacetone using an organic solvent (e.g., dichloromethane).
- Distill the organic solvent to obtain pure acetylacetone.

Additional information (procedure and reaction conditions):

- ***Reaction Vessel:***
  Use a round-bottom flask equipped with a magnetic stirrer and a reflux condenser.

- ***Solvents***:
  Inert solvent: Use a non-reactive solvent like n-heptane (50-100 mL) for the initial reaction mixture.
  Organic solvent for extraction: Dichloromethane (DCM) is commonly used for extraction (50-100 mL).

- ***Temperature***:
  1. Maintain a cool temperature (around 10°C) during the addition of butyl acetate to the sodium butoxide solution.
  2. Keep the reaction temperature below 40°C while adding acetone.
  3. Increase the reaction temperature to 80-85°C and maintain it for several hours (typically 3 hours) after adding all the reactants.

- ***Concentration***:
  The concentration of reactants is not typically critical for this reaction. However, a stoichiometric ratio (1:1:4) of sodium butoxide (NaOBu): butyl acetate: acetone is commonly used.

- ***Time***:
  Allow the reaction mixture to stir at the elevated temperature (80-85°C) for several hours (typically 3 hours) for optimal product yield.

- ***Safety:***
  1. Conduct the reaction in a well-ventilated fume hood due to the use of flammable organic solvents (acetone, butyl acetate, dichloromethane).
  2. Handling chemicals requires wearing appropriate personal protective equipment (PPE) such as gloves, safety goggles, and a lab coat.
  3. Sodium butoxide is a strong base and can cause skin irritation. Handle it with care and avoid contact with skin and eyes.

References:

***Theory for production*:**
Link1: RU2707190C1 - Acetylacetone production method - Google Patents
Link2: https://www.nanotrun.com/article/preparation-and-application-of-acetylacetonate-i00087i1.html
Link3: https://www.chemicalbook.com/Article/Introduction-of-Acetylacetone.htm

Basic Skeleton of Claisen reaction
https://chem.libretexts.org/Bookshelves/Organic_Chemistry/Supplemental_Modules_(Organic_Chemistry)/Reactions/Reactivity_of_Alpha_Hydrogens/Claisen_Reactions

Other references
https://www.orgsyn.org/demo.aspx?prep=CV3P0016
https://www.organic-chemistry.org/namedreactions/claisen-condensation.shtm
acetylacetone.synthesis.pdf (mdma.ch)

List the contributions of each author:

- Roshan Patil came up with the process we will use on the industrial level and also worked on different processes that are possible for acetylacetone manufacturing although those method came out to be limited only to the laboratory i.e. was not scalable.

Name	Roll No	Signature
CEO Name - Sidhant Thalor	221055	Sidhant
First Author Name - Roshan Patil	220760	Roshan

Nature of Invention: Chemical molecule and synthesis route

Applicant: National Chemicals Limited [NCL]

Inventors: Akshat Shrivastav, Sidharth Budania

Chemical Formula: $C_2H_3ClO_2$

Chemical Name: Monochloroacetic acid

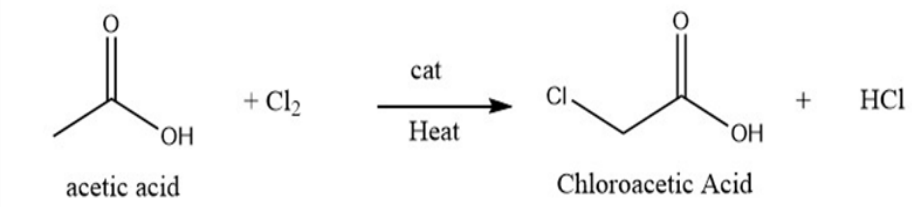
Chemical synthesis routes:

PREPARATION OF MONOCHLOROACETIC ACID (MCAA) USING GLACIAL ACETIC ACID:

Raw Material:

- Acetic acid
- Acetic anhydride
- Chlorine gas
- Catalytic promoters (H_2SO_4 & $FeCl_3$)

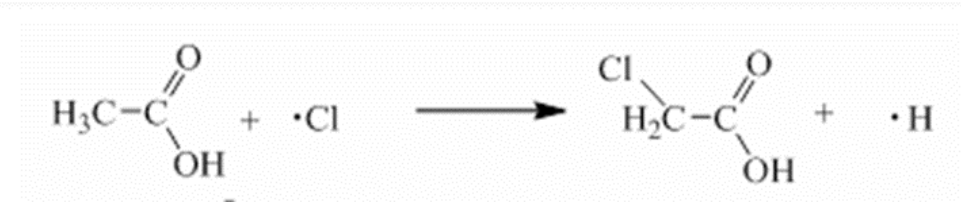
Reaction:



Reaction Temperature: 105℃ to 110℃
Reaction Time: 6 to 7 hrs
Yield: 89.5%
Purity: 93.8% (in product mixture)
97.5% to 99.1% (After crystallization and separation)

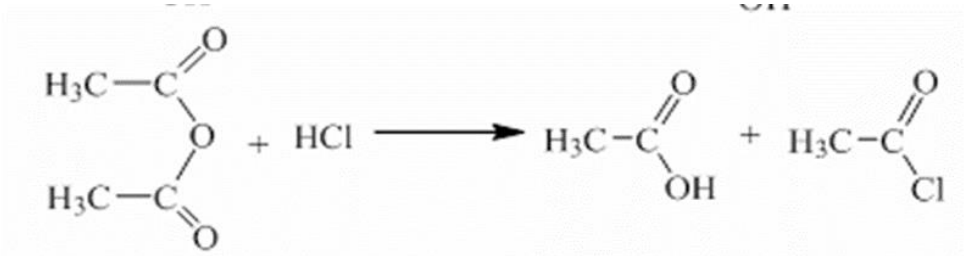
Mechanism:

A) Radial Mechanism

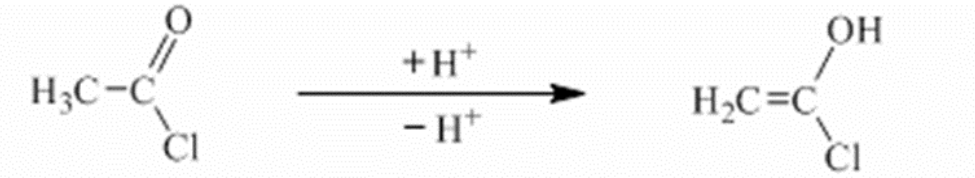


B) Ionic Mechanism

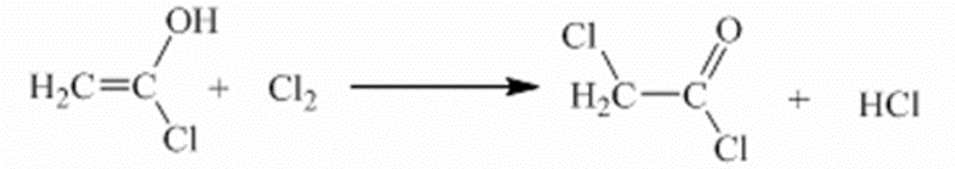
acetic anhydride conducted initially and formed acetyl chloride



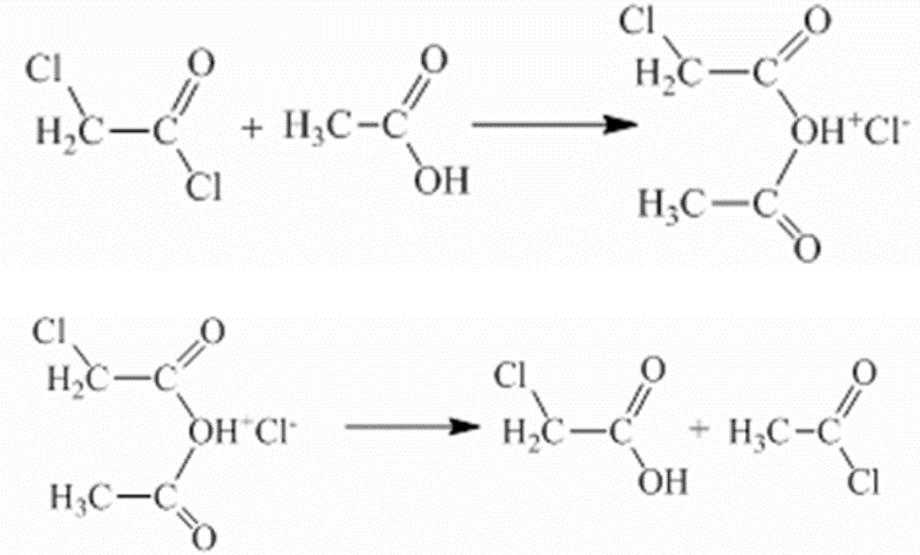
acetyl chloride conducted the enolization and formed 1-chloro,1-ethene-1-ol



the double bond in 1-chloro,1-ethene-1-ol reacts with chlorine and forms chloroacetyl chloride



the -OH and -Cl exchange reaction generats monochloroacetic acid



Radical mechanism in the absence of a catalyst, and the dichloroacetic acid was formed consecutively from monochloroacetic acid. While with the presence of catalyst, the mechanism was changed, and the monochloroacetic acid formation was enhanced, but the dichloroacetic acid formation was prohibited.

Side Reaction:

Reaction of MCAA and acetyl chloride to dichloroacetic acid

$ClCH_2COCl + ClCH_2COOH \longrightarrow Cl_2CHCOOH + CH_3COCl$

Purity: 3.86% (in product mixture)
0.4%≤DCA≤1.0% (After crystallization and separation)

Procedure:

- The chlorination of acetic acid was carried out in a glass tube equipped with a magnetic stirring apparatus.
- The glass tube was heated by an oil bath heater with a temperature controller.
- The chlorine gas was metered by a rotameter to disperse into the reaction mixture.
- A reflux condenser equipped with low temperature cooling circulating pump was placed on the top of the reactor.
- The acetic acid to be chlorinated was placed in the reaction vessel. The slightly excess chlorine feed was introduced, and the liquid phase was heated to the desired reaction temperature. A certain amount of acetic anhydride was added.
- Crystallize to purify the extracted monochloroacetic acid product

ALTERNATE PREPARATION OF MCAA USING HYDROLYSIS OF TRICHLOROETHYLENE

Raw Material:

- Trichloroethylene
- Sulfuric Acid (catalyst)
- Water

Reaction:

CCl_2=CHCl + 2 H_2O → $ClCH_2COOH$ + 2 HCl

Reaction Temperature: 130℃ to 140℃
Reaction Time: 2-5 Days for Overall production (batch process)
Yield: 89.5%
Purity: >99%

Mechanism:

Step 1: Hydrolysis of Trichloroethylene
Trichloroethylene (C2HCl3) undergoes hydrolysis to form chloral (CCl3CHO):
C2HCl3 + H2O → CCl3CHO + 2HCl

Step 2: Oxidation of Chloral
Chloral is then oxidized to form chloral hydrate (C2H3Cl3O2) using an appropriate oxidizing agent, such as hypochlorous acid (HClO):
CCl3CHO + HClO → C2H3Cl3O2 + HCl

Step 3: Hydrolysis of Chloral Hydrate
Chloral hydrate undergoes hydrolysis to form monochloroacetic acid (MCAA) and hydrochloric acid:
C2H3Cl3O2 + H2O → CH2ClCOOH + 2HCl

Procedure:

1. Hydrolysis of Trichloroethylene:
Trichloroethylene (TCE) is typically hydrolyzed in the presence of water and a catalyst. The reaction is usually carried out in a reactor vessel equipped with agitation and temperature control. Sulfuric acid or hydrochloric acid is used as a catalyst. The hydrolysis reaction produces chloral (trichloroacetaldehyde) and hydrochloric acid.

2. Oxidation of Chloral:
Chloral produced from the hydrolysis step is then oxidized to chloral hydrate. This step typically involves the addition of an oxidizing agent such as chlorine gas or hypochlorous acid. The oxidation reaction may be carried out in a separate reactor vessel under controlled conditions of temperature and pressure.

3. Hydrolysis of Chloral Hydrate:
Chloral hydrate is hydrolyzed to form monochloroacetic acid (MCAA) and hydrochloric acid. This reaction can be performed by adding water to the chloral hydrate and heating the mixture under reflux conditions.

4. Purification and Recovery:
The trichloroethylene method produces highly pure chloroacetic acid free of di- or trichloro acetic acid. The purification procedure consists of separation from trichloroethylene, sulphuric acid and water. Despite the purity of the chloroacetic acid formed, this method has fallen into disuse because of the high cost of trichloroethylene and the large amount of HCl produced.

References: ·

US Patent for Method of industrially producing monochloroacetic acid Patent (Patent # 10,494,325) : https://patents.justia.com/patent/10494325

Mechanism of chlorination process: From acetic acid to monochloroacetic acid and byproducts using acetic anhydride as catalyst: http://web.icf.ro/rrch/

https://www.researchgate.net/publication/289269184_New_method_for_synthesizing_monochloroacetic_acid

Process for the preparation of monochloroacetic acid
https://patents.google.com/patent/US7135597B2/en

https://www.sciencemadness.org/smwiki/index.php/Chloroacetic_acid

https://chemcess.com/chloroacetic-acid/
https://pubchem.ncbi.nlm.nih.gov/compound/Chloroacetic-acid#section=Pharmacology-and-Biochemistry

https://application.wiley-vch.de/books/sample/3527334777_c01.pdf

List the contributions of each author:

- Akshat Shrivastav carried out the literature search and found the reaction steps and product yield for the Preparation of MCAA using Glacier Acetic Acid.
- Sidharth Budania carried out the literature search and found the reaction steps and product yield for the Preparation of MCAA using hydrolysis of trichloroethylene.

Name	Roll No	Signature
CEO Name - Sidhant Thalor	221055	Sidhant
First author Name - Akshat Shrivastav	220103	Akshat
Second author Name - Sidharth Budania	221057	Sidharth