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:

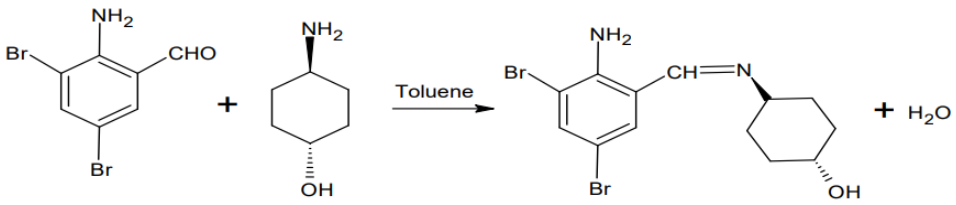
PREPARATION OF AMBROXOL USING TOLUENE

Raw materials used:

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

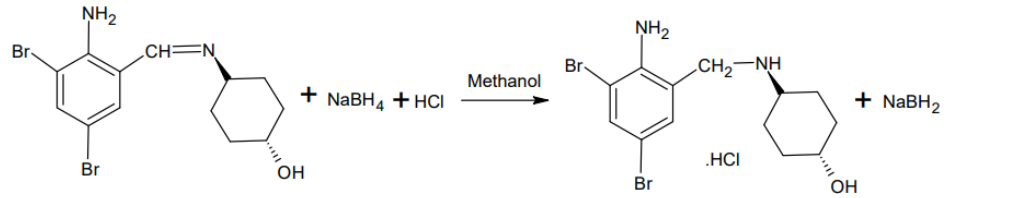
Reactions involved:

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.

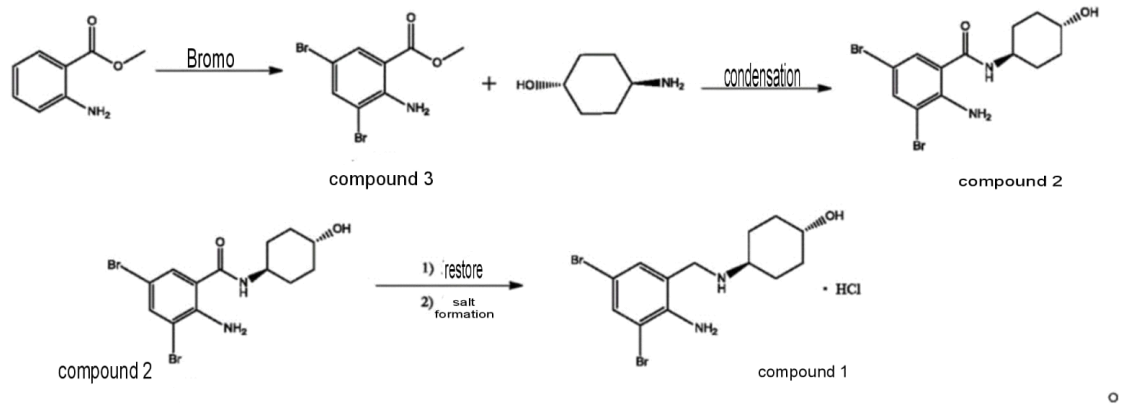
Operational steps:

- 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