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Synthesis of Cysteamine Hydrochloride by High Pressure Acidolysis of 2-Mercaptothiazoline

YING CUI, SHIYU TAN, ZIPING LUO and LICHUN DONG*
School of Chemistry and Chemical Engineering,
Chongqing University, Chongqing 400044, P.R., China
Fax/Tel: (86)(23)65111179; E-mail: lcdong72@gmail.com

The synthesis of cysteamine hydrochloride by high pressure acidolysis of 2-mercaptothiazoline was investigated and the result showed that the high pressure acidolysis can significantly increase the reaction rate as well as the product yield. Characterization by melting point, purity analysis, IR and ^{1}H NMR proved that the synthesized product is cysteamine hydrochloride with purity as high as 98.9 %. The reaction pressure and molar ratio between the reactants were demonstrated to have significant impacts on the product yield. The optimum conditions for the acidolysis reaction obtained *via* a group of orthogonal experiments are: reaction pressure, 0.3 MPa; mole ratio between 2-mercaptothiazoline to HCl (20 wt %), 1:5; reaction time, 7 h. Under the optimum conditions, the yield of cysteamine hydrochloride can reach 95.6 %.

Key Words: Cysteamine hydrochloride, 2-Mercaptothiazoline, High pressure acidolysis.

INTRODUCTION

As a kind of useful raw material and pharmaceutical intermediate, cysteamine hydrochloride (CSH) is finding many applications in medicines[1,2], cosmetics[3] animal feed additives[4-7] *etc*. The current preparation methods of CSH include extraction from animal hairs and chemical synthesis[8-12]. In extraction method, animal hair was first hydrolyzed to obtain homocysteine, which is further reduced and decarboxylated to get the product. This method is time-consuming and not suitable for mass production. Moreover, the extraction method was forbidden in European Union owing to the outbreak of bovine spongiform encephalopathy. The chemical synthesis of CSH has five routines, namely, ethanolamine-hydrogen bromide method, ethanolamine-sulfuric acid-cyclohexylamine method, hydrogen sulfide-aziridine method, ethanolamine-sulfuric acid-thiosulfate method and ethanolamine-sulfuric acid-thiazoline method. Among these routines, the ethanolamine-sulfuric acid-thiazoline method has emerged as the conventional process to mass-produce CSH in industry owing to its advantages of mild operating conditions, low cost, *etc*. In this method, ethanolamine first reacts with sulfuric acid to produce 2-aminoethyl sulfate, which further reacts with carbon disulfide to generate 2-mercaptothiazoline (2MT). The CSH product is then obtained by hydrolyzing 2MT in an acidic or alkali solution. However, although having a higher CSH yield than alkali hydrolysis; the CSH yield for acidolysis of 2MT at atmospheric pressure is only around 70 %. Moreover, it takes more than 160 h for the completion of the reaction.

The acidolysis of 2MT is an exothermic reaction, increasing temperature can accelerate the reaction rate as well as shift the reaction equilibria to the desired direction of high CSH yield. However, the reaction temperature is correlated with the reaction pressure; the reaction temperature must be slightly below the saturation temperature of water at the corresponding pressure to keep water in the liquid state. In the present study, the high pressure acidolysis of 2MT to CSH was investigated, the results showed that the high pressure acidolysis can significantly increase the reaction rate as well as the product yield. Characterization by melting point, purity analysis, IR and ^{1}H NMR proved that the synthesized product is CSH with purity as high as 98.9 %. Under the optimum operation conditions obtained *via* a group of orthogonal experiments, the yield of CSH can reach 95.6 %.

EXPERIMENTAL

Product synthesis: 2-Mercaptothiazoline was synthesized in laboratory and mixed with HCl solution (20 wt %, Analytical Grade, Quandong Chemical Reagent Plant, Chongqing, China) in a conical flask of 500 mL. The conical flask was heated in an autoclave to perform the synthetic reaction with reflux at a controlled pressure for several hours. The reaction was showed in eqn. 1.

$$C_3H_5NS_2 + 2H_2O + HCl \xleftrightarrow{H^+} C_2H_7NS{\cdot}HCl + H_2S + CO_2 \qquad (1)$$

After the reaction, the reactive mixture was vacuum-distillated for 1 h to remove water and HCl. The obtained raw-product was dried in a vacuum oven at 60 ºC for 4 h, followed by natural drying in a basin for 8 h to obtain the final light yellow product. The quantity of CSH product was measured and its yield (based on 2MT) was calculated according to eqn. 2.

$$\text{CSH Yield (\%)} = \frac{\text{Quantity of CSH product}}{\text{Quantity of 2MT} \times \frac{113.60}{119.20}} \times 100 \qquad (2)$$

The purity of CSH is determined by the method of iodimetry. In the process, the sulfhydryl group in CSH is oxidized by iodine, while the quantity of iodine before and after the reaction can be determined using titration method to calculate the amount of CSH by reported method[13]. Melting point of the product is determined by using XRC21 microscopic melting point apparatus (Sichuan University Scientific Instrument Co. Ltd., Chengdu, China). ^{1}H NMR spectrum of CSH solved in D_2O was analyzed using a Bruker AV50 NMR spectrometer (Swiss). The IR spectrum of CSH was recorded on a MAGMA-IR550 spectrometer (Nicolet Company, USA) using KBr pellet.

RESULTS AND DISCUSSION

In 2-mercaptothiazoline (2MT) (Fig. 1), the sulphur atom in the thiazoline ring is nucleophilic due to its strong electronegativity. In an acidic solution, it very vulnerable to be attacked by a H^+ ion, leading to the cleavage of C-S bond. On the other hand, the nitrogen atom in 2MT also has a pair of lone-pair electrons and therefore, it is also prone to accept a proton in an acidic solution, causing the rupture of C=N bond. According to the above analysis, the hypothesized mechanism of the open-loop and hydrolysis reaction of 2MT in an acidic solution is illustrated in Fig. 1.

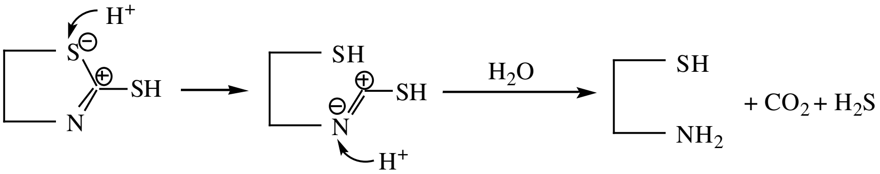


Fig. 1. Scheme of the reaction procedures of CSH synthesis

For the hydrolysis of 2MT, the cleavage of C=N bond is the controlling step since it is much more stable than the C-S bond. Consequently, the hydrolysis of 2MT at an atmospheric pressure takes more than 160 h with low yield. In this study, the high-pressure acidolysis of 2MT to CSH is investigated in order to increase the reaction temperature. Moreover, the hydrolytic reaction of 2MT is accompanied with the generation of H_2S and CO_2, whose constant if takenout from the reactive system is beneficial to shift the equilibrium to the desirable direction. Thus in the experimental set-up, an alkali absorption device was equipped to remove the generated gas continuously from the system with the aim to move the reaction equilibrium to the direction of high CSH yield.

Product characterization

Melting point and purity analyis: As one of the basic data, the melting point can give a primary judgment of an organic compound. The average melting point of product is determined to be 70.4 ºC, which is well coincident with the literature value of 70 ºC. The purity test showed that the purity of the product can be as high as 98.8 %.

^{1}H NMR Analysis: The ^{1}H NMR testing result of CSH product (Fig. 2) shows only 2 groups of peaks in the spectrum with the intesity ratio between them close to 1:1. The peaks are atrributed to the two groups of hydrogen atoms in two $-CH_2-$ groups, while the hydrogen atoms in $-NH_2$ and -SH are deuterated in D_2O solution. Consquently, no corresponding peaks apear in the spectrum. Since, the electronegativity of sulphydryl group is stronger than that of amine group, the peak at smaller chemical shift (δ = 2.697 ppm) is beleived to be attributed by hydrogen atoms in $-CH_2-$ group connecting the amine group, *i.e.* the α-methyl group, whereas the peak at δ = 3.067 is corresponding to the β-methyl group.

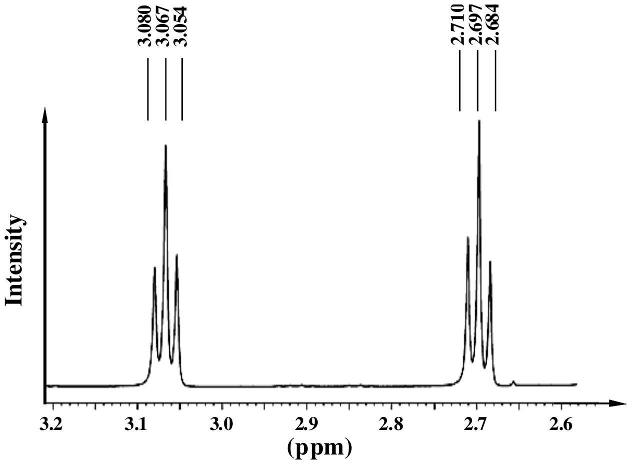


Fig. 2. ^{1}H NMR spectrum of the product

IR spectra: Fig. 3 compared the IR spectra of the standard CSH sample (line A) and that of the product of high pressure acidolysis (line B). The two spectra of the two samples are very close and the trivial difference between the two spectra is within the tolerance of testing error, which further confirmed that the obtained product is CSH with high purity. In the spectra, the vibration peaks corresponding to -NH_2 include: 3417 cm^{-1} (asymmetric stretching), 3007 cm^{-1} (symmetric stretching). The peaks close to 2000 and 1600 cm^{-1} are due to the salt formed by CSH with HCl (-NH_3^+). The peak attributed by stretching of -CH_2- groups appears around 2950 cm^{-1} and its bending adsorption peaks apears around 1450 cm^{-1}. The weaker peak at 2488 cm^{-1} is owing to the stretching vibration of -SH group. Moreover, the peak around 1100 cm^{-1} is corresponding to the stretching vibration of C-N bond.

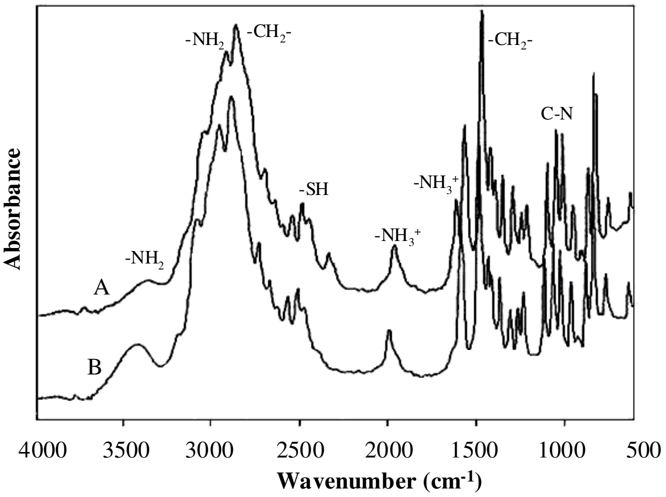
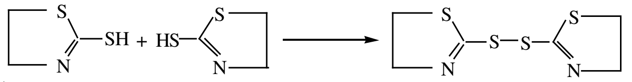


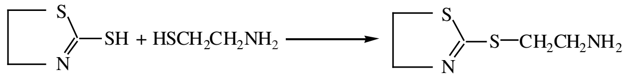
Fig. 3. IR spectra the standard CSH sample (A) and the product (B)

Affecting factors of the synthesis reaction

Reaction pressure: Fig. 4 shows the variation of the product yield based on 2MT with the reaction pressure. It can be seen that the yield first increases with an increase in reaction pressure, reaching a maximum at 0.3 Mpa, then decreases with a further increases in reaction pressure. At high pressure, the reaction temperature can thereupon be increased owing to the increase of saturated temperature of water. It can accelerate the reaction rate as well as shift the reaction equilibria to the direction of higher CSH yield, therefore, the CSH yield first increases with an increase in reaction pressure. However, when pressure is too high or reaction time is too long, the side reactions showed in Fig. 5, mainly crosslinking reaction *via* -SH bond, would be significantly intensified, leading to the decrease yield of CSH as well as the purity of the product.



(3)



(4)

$$HSCH_2CH_2NH_2 + HSCH_2CH_2NH_2 \longrightarrow NH_2CH_2CH_2S-SCH_2CH_3NH_2 \quad (5)$$

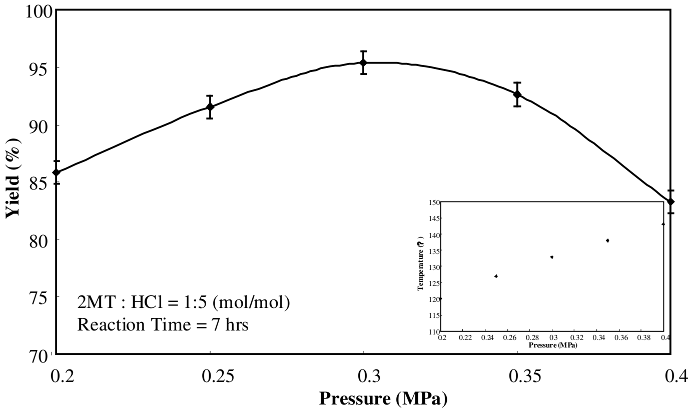


Fig. 4. The product yield *versus* reaction pressure, the corresponding reaction temperature at different reaction pressure is showed in the inset

Molar ratio between 2MT and HCl: Among the two raw materials for the CSH production, 2MT is more expensive than hydrochloric acid. Therefore, it is economical to increase the conversion ratio of 2MT (CSH yield based on 2MT) as high as possible by increasing the dose of hydrochloric acid. In this study, the CSH yield in different molar ratios was studied. The result (Fig. 5) shows that the optimum molar ratio between HCl and 2MT is around 5. When the molar ratio is less than 5 the CSH yield increases with an increase in the molar ratio, while when the molar ratio is larger than the optimum value, the CSH yield decreases with further increase in the molar ratio. High HCl concentration can move the equilibrium of the synthesis to the right direction, resulting in the increase of CSH yield. However, too much HCl can enhance the undesired side reactions *e.g.,* the rupture of C-S bond of 2MT, which would cause the decrease in CSH yield and purity.

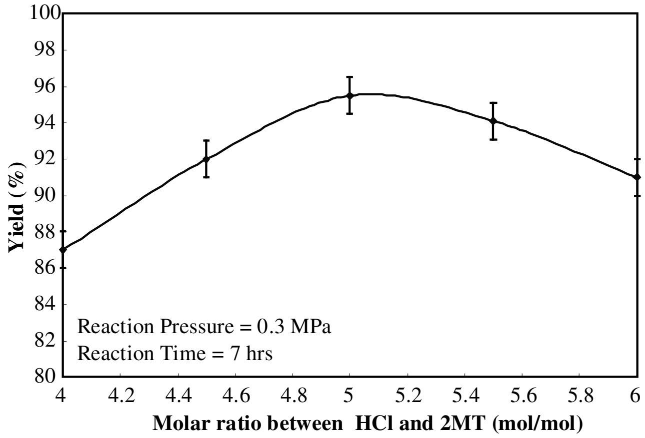


Fig. 5. Effects of material rate of 2-mercaptothiazoline to hydrochloric acid

Optimum operating conditions: On the basis of single-factor experiments, the optimum conditions for the production of CSH *via* high-pressure 2MT acidolysis were investigated *via* a group of orthogonal experiments (L_{16}, 3^4). The optimum operating conditions obtained are: reaction pressure, 0.3 MPa; molar ratio between 2MT and HCl (20 wt % aqueous solution), 1:5; reaction time, 7 h. Under the above operating conditions, the yield of CSH based on 2MT can reach 95.6 % and the purity is up to 98.9 %.

Conclusion

This paper investigated the synthesis of CSH by high pressure acidolysis with the aim to decrease the reaction time as well as increase the product yield. The synthesized product was characterized by melting point measurement, purity analysis, IR and ^{1}H NMR, the result proved that the synthesized product is CSH with purity as high as 98.9 %. The reaction pressure and molar ratio between the reactants have demonstrated to have significant impacts on the product yield. The optimum conditions for the acidolysis reaction obtained *via* a group of orthogonal experiments are: reaction pressure, 0.3 MPa; mole ratio between 2MT to HCl (20 wt %), 1:5; reaction time, 7 h. Under the optimum conditions, the yield of CSH can reach 95.6 %.

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