International Journal of Sciences: Basic and Applied Research (IJSBAR)

ISSN 2307-4531
(Print & Online)

http://gssrr.org/index.php?journal=JournalOfBasicAndApplied

A Novel Synthesis of Cefuroxime from 7-amino Cephalosporanic Acid (7-ACA)

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Abstract

Cefuroxime, a second-generation cephalosporin antibiotic, was synthesized from 7-amino cephalosporinic acid (7-ACA) and (*Z*)-2-methoxyimino-2-(furyl-2-yl) acetic acid ammonium salt (SMIA) as starting materials. The total yield of cefuroxime synthesized via the 4-step scheme was 42%. The novel feature of this study was the use of oxalyl chloride activating reagent which replaced phosphoryl chloride in the activation of SMIA. The result showed that the yield was 90% in the reaction time of 1.5 hours. Especially, this synthesis can be considered as a green process because the waste water only contained NH_4Cl, CO and CO_2 non-toxic compounds.

Keywords: 7-ACA; SMIA; decarbamoyl cefuroxime acid; cefuroxime.

1. Introduction

Cefuroxime i.e., (6R,7R)-7-[2-furanyl-(Z)-2-methoxyimino]acetamido-3-carbamoyloxymethyl-3-cephem-4-carboxylic acid (1), is a valuable semi-synthetic second-generation cephalosporin, which has antibiotic activity in the broad-spectrum of gram-positive and gram-negative microorganisms. Cefuroxime and its salts are principally as injectable antibiotics because they are poorly absorbed from the gastro-intestinal tract. The absorption can be improved thanks to the conversion of the free 4-carboxylic acid group to its corresponding esters.

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It can be explained by the hydrolysis of esters in-vivo, therefore the absorption of cefuroxime in the gastro-intestinal increased. Cefuroxime was synthesized and marketed since the 1980s. There are numerous of publications on the synthesis of cefuroxime antibiotic [2-7]. US. Patent. No 2004/0092735A1 described the process for preparation of cefuroxime in the presence of DMAC/DMF solvent or a mixture thereof at the temperature in the range of -40 ^{o}C to 0 ^{o}C, the activation of fur-2-yl methoxy imino acetic (the activating reagent is $POCl_3$). Additionally, cefuroxime acetyl was prepared from cefuroxime acid using RCNO (chlorosulfonyl isocyanate). The product obtained from this synthesis was purity, as well as the reaction total yield was high, around 42%. However, the waste solvent including phosphoric acid, hydrochloric acid and ammonium chloride was toxic and the synthesis process was not green. Synthetic communications Vol 33, No.14, pp 2475-2482 (A novel and Efficient Synthesis of (6R, 7R)-7-Amino-3-hydroxymethyl Cephalosporanic Acid: A Versatile Precusor of Cefuroxime Acid) described the process for preparation of cefuroxime using the combined reagents [triethyl amine/tetrabutyl ammonium hydroxide (TBAH)] at the ambient temperature. The total yield improved, but the activation reagent (PCl_5/DMF) was also not green.

In this study, we research on the preparation of cefuroxime from 7-ACA and SMIA (fur-2-yl methoxyimino acetic) in the presence of DMAC/DMF mixture in the activation of SMIA [the activation reagent is OXC (oxalyl chloride)] and the preparation of cefuroxime axetyl from cefuroxime acid using RCNO (chlorosulfonyl isocyanate). The study shows that the total yield of cefuroxime synthesized via the 4-step scheme is 42%. The process is good and green with the shorter time and the improved yield, the values are 1.5 hours and 90%, respectively. Moreover, the waste water only contains NH_4Cl, CO and CO_2 non-toxic compounds. The theme aims to find out the appropriate procedure for preparation of cefuroxime at the laboratory-scale in Vietnam.

2. Experimental

2.1. Materials and apparatus

7-ACA (99% purity, Meyer Shanghai, China), SMIA (99% purity, Meyer Shanghai, China), and triethylamine (TEA, 99.5% purity, Thermo scienctific, India), *N*,*N*-Dimethylacetamide (99% purity, Sigma-Aldrich, USA). The other solvents were purchased from Chemsol Vina Co. Ltd, Vietnam. The purity of the products were determined via Agilent HPLC-Model G1329A. Melting points were determined by using an electro thermal 2000 apparatus without extra correction. The NMR spectra were done with Brucker Avance (500 MHz) instrument using TMS as an internal standard. Infrared spectra were recorded via FTIR Shimadzu 8201 spectrophotometer. Mass spectra were run on HPLC/MS Agilent-MSD-Trap-SL mass spectrometer using API mode.

2.2. Production of cefuroxime

Preparation of (*Z*)-2-methoxyimino-2-(furyl-2-yl) acetyl chloride (SMIA-Cl) from SMIA

This process is shown in Diagram 1.

A mixture of dimethylacetamide (14.0 mL), dichloromethane (2.0 mL), and dimethylformamide (2.0 mL) were introduced in a dry flask, adding SMIA (2.0 grams, 10.7 mmol) and cooling the mixture down to -40 °C. Then,

adding oxalyl chloride (OXC, 3.4 grams, 22.2 mmol) and stirring at -20±2 ^{o}C for 30 minutes. The mass was continuously cooled and stirred at -30 ^{o}C for 60 minutes and remained at this temperature for the next reaction.

Preparation of (6R,7R)-7-amino-3-hydroxymethyl-3-cephem-4-carboxylic acid (7-AHCA) from 7-ACA

The suspension of 7-ACA (2.5 g, 9.2 mmol) was introduced in a mixture of methanol (20 mL) and water (20 mL). Adding sodium hydroxide (1.5 g, 0.022 mol in 10 mL water) at 5 ^{o}C for 10 minutes to obtain clear solution. The temperature was maintained at -40 ^{o}C for 1.0 hour. After the reaction had finished, pH of the mixture was adjusted to 4.0 by using HCl dilute solution. The product was filtered, sequentially washed by distill water, dichloromethane, and dried at 45 ^{o}C in vacuum to obtain pure 7-AHCA. The total yield of reaction is 80.4%.

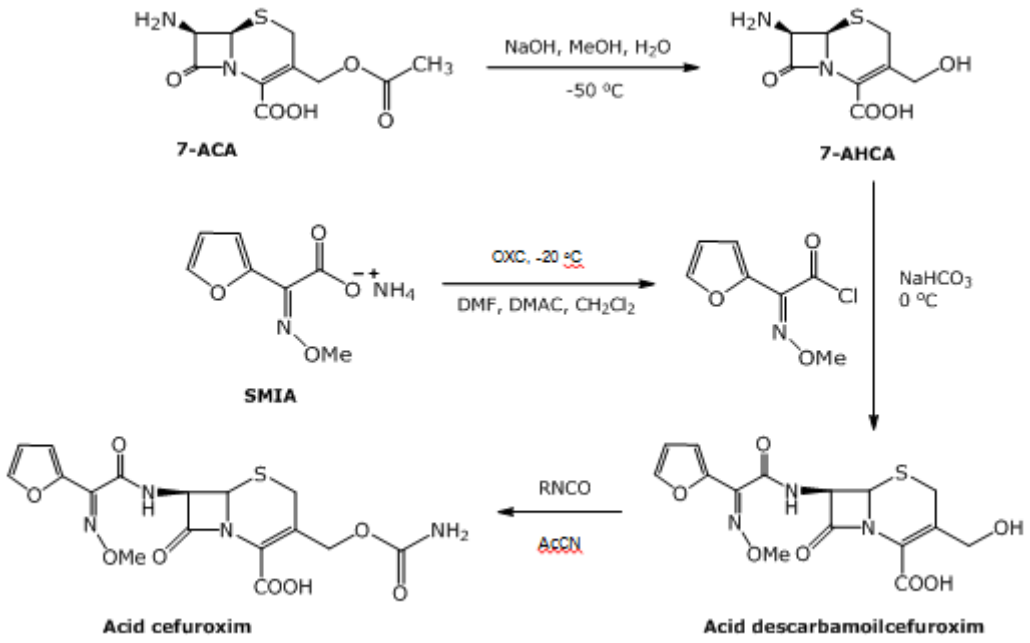

Figure 1: The process for preparation of cefuroxime from 7-ACA and SMIA

Preparation of descarbamoyl cefuroxime acid from 7-AHCA and SMIA_Cl

A mixture of water (30 mL) and methanol (30 mL) were introduced in another flask, 7-AHCA (2.0 grams, 8.7 mmol) was added and cooled to -40 ^{o}C. Adding sodium hydroxide solution (2.0 grams in 10 mL water) at -10 ^{o}C in 10 minutres to obtain clear solution (7-AHCA solution). After the reaction had finished, pH of the mixture was adjusted in the range of 7.0 to 8.0 by using HCl dilute solution. The temperature of reaction raised to 0 ^{o}C after adding the satured sodium bicarbonate solution (20 mL) and SMIA_Cl solution (prepared in the step 1) at 0-2 ^{o}C. The mixture was refluxed for 30 minutes. After the reaction had finished, pH of the mixture was adjusted to 2.0 by using HCl dilute solution. The product was filtered, and sequentially washed by distill water, dichloromethane, and dried at 45 ^{o}C in vacuum to obtain descarbamoyl cefuroxime acid. The product was in white powder (71.3% yield; 90.9% purity).

Preparation of cefuroxime acid from descarbamoyl cefuroxime acid

To introduce the stirred suspension of descarbamoyl cefuroxime acid (2.5 grams, 0.0065 mol) in dry acetonitrile (12.5 mL), the adding chlorosulfonyl isocyanate (CSI, 2.0 mL, 0.0229 mol) at 0-5 ^{o}C in 15 minutes. The mixture was stirred at 0-5 ^{o}C for 60 minutes. The clear solution of the reaction mixture was poured into cold water (25 ml) and continuously stirred at 25 ^{o}C for 60 minutes. The reaction mixture was extracted using ethyl acetate (50 mL) after adjusting pH to 7.5 by ammonia solution (25%) at 5 ^{o}C. The aqueous phase was stirred with the presence of activated carbon (1.0g) in the range of pH form 5.0 to 5.5 at 5 ^{o}C. Removing activated by filtering method, then, the filtrate was acidified to pH 2.0 using HCl solution 10% at 0-5 ^{o}C. The solid product was washed by acetonitril-water mixture (the ratio of 1 to 4, done 3 times) and dried at 40 ^{o}C in vacuum to obtain 3.2 grams of cefuroxime acid. The total yield was 72%.

3. Results and discussion

3.1. Preparation of SMIA-Cl from SMIA

SMIA reagent is activated into chloride acid compound, SMIA-Cl. SMIA reacts with oxalyl chloride (the molar ratio of 1 to 1) in a solvent-solute mixture consisting of DMAC, DMF, and MC (the volume ratio of 7:1:1). SMIA_Cl solid obtained from the reaction is pale yellow. The use of oxalyl chloride in the activation reaction of SMIA is a novel synthesis of cefuroxime. The process obtains a high total yield (around 90%) and is considered as a green synthesis because of the non-toxic waste water consisting of NH_4Cl, CO and CO_2 (Pandurang Balwan, 2004; Santo Kumah Sing, 2003).

3.2. Preparation of 7-AHCA from 7-ACA

Hydrolyzing 7-ACA in sodium hydroxide solution and methanol/water solvent at -40 ^{o}C for 1 hour to convert —CH_2OCOCH_3 group into —CH_2OH group. 7-AHCA product is high purity and the total yield is 80.4%. The results are shown in Table 1.

Table 1: The effect of the molar ratio of 7-ACA to NaOH in the synthesis of 7-AHCA

The molar ratio of 7-ACA:NaOH	The molar of substrate 7-ACA (mol)	The molar of product isolated (mol)	The yield (%)
1:1.2	0.009	0.0076	73.2
1:1.3	0.009	0.0079	76.8
1:1.4	**0.009**	**0.0083**	**80.4**
1:1.5	0.009	0.0078	74.0

Spectral data used to determine 7-AHCA

IR (KBr): νmax cm^{-1} 3397 (νO-H); 3174 (νN-H); 3003 (νC-H); 1797 (νC=O, β-lactam); 1619 (νC=O, -COOH).

MS (m/z): $[M-H]^+$ =229.13.

^{1}H-NMR (DMSO-d6), δ (ppm): 4.91 (d, 1H, -C**H**-CH-S-, *J*=5 Hz); 4.71 (d, 1H, -CH-C**H**-S-,*J*=5 Hz); 4.19-4.23 (dd, 2H, -C-C**H**$_2$-OH, J_1=13.5 Hz, J_2=*18* Hz); 3.54-3.57 (d, 1H, -S-C**H**H-, *J*=15 Hz); 3.46-3.49 (d, 1H, -S-CH**H**-, *J*=15 Hz).

3.3. Preparation of descarbamoyl cefuroxime acid

The nucleophile acylation of 7-AHCA with SMIA-Cl reagent creates decarbamoyl cerfuroxime acid. 7-AHCA plays a role of a nucleophilic agent with a lone pair of electrons on N atom of –NH_2 group, while SMIA-Cl contains C=O group acting as a strong polarized group. After reacting, -Cl group is detached from the acid, the pH of solution had to adjust in the range of 7.0 to 7.5 to prevent the formation of hydrogen chloride. Moreover, at the low pH, 7- AHCA may be in solid powder and cannot react.

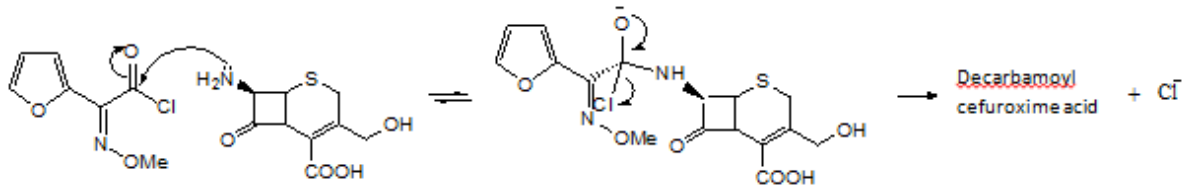

Figure 2: The reaction mechanism of acylation of 7-AHCA with SMIA-Cl

Descarbamoyl cefuroxime acid synthesized via this process was a white solid, with the total yield of 71.3% and the purity of 90.9%. The structure and component of the product were identified by ^{1}H-NMR spectrum, HPLC-MS and HPLC-UV.

Spectra data to determine of Descarbamoyl cefuroxime acid

IR (KBr) νmax cm^{-1} 3571.9 (νO-H); 3392.6; 3234.4; 1764.7 (β-lactam, νC=O); 1728.1; 1681.8; 1643.2, 1569.9 $cm^{-1.}$

MS (m/z): $[M-H]^-$ = 380.06.

^{1}H-NMR (DMSO-d6), δ (ppm): 3.76-3.86 (dd, 2H, -S-C**HH**-, J_1=9 Hz, J_2=27.5 Hz); 3.90 (s, 3H, -OCH_3); 5.05 (s, 2H, -C**H**$_2$OH); 5.19-5.20 (d, 1H, -C**H**-S-, *J*=5 Hz); 5.96-5.97 (d, 1H, -C**H**-CH-S, *J*=5 Hz); 6.63-6.64 (dd, 1H, -HC=C**H**-CH=, J_1=2 Hz, J_2=3.5 Hz); 6.69-6.70 (d, 1H, -**H**C=CH-CH=, *J*=5 Hz); 7.84-7.842 (d, 1H, -C**H**=CH-CH=,*J=2* Hz); 9.80 (s, 1H, -N**H**-).

3.4. Preparation of cefuroxime acid from decarbamoyl cefuroxime acid

In this step, the cefuroxime acid was synthesized from decarbamoyl cefuroxime acid and chlorosulfonyl isocyanate (CSI) in the range of 0 to 5 °C, in CH_3CN solvent (in this case, –CH_2OH group converted to –CH_2OCONH_2 group). The molar ratio of decarbamoyl cefuroxime acid to CSI was 1:2. The amount of water

was extracted by ethyl acetate solvent. The reaction mixture was hydrolyzed in ammoniac solution 25% in the range of pH from 7 to 7.5, then, it was acidified by hydrochloric acid solution to decrease pH down to 2.0. The cefuroxime acid crystal was formed. The molar ratio of decarbamoyl cefuroxime acid to CSI was researched and shown in Table 2.

Table 2: The effect of the molar ratio of descarbamoyl cefuroxime acid to CSI

The molar of CSI to Descarbamoyl cefuroxim acid	The weight of product (gr)	The purity of product (%)	Yield (%)
1.5 : 1.0	2.20	71	56
2.0 : 1.0	**2.21**	**90**	**72**
2.5 : 1.0	2.10	84	62
3.0 : 1.0	2.40	64	54

The Table 2 shows that the amount of cefuroxime increases when the molar ratio of decarbamoyl cefuroxime acid to CSI increases. The yield of the reaction is quite good if comparing to other researches (*US Patent* 0092735A1). At the ratio of 2.0 to 1.0, the product has the highest purity and the yield is 72% which can be accepted. When the ratio of CSI to decarbamoyl cefuroxime acid is over of 2.5 to 1.0, both the yield and the purity decrease.

Spectra data to determine of cefuroxime acid

IR (KBr) νmax cm^{-1} 3482.5; 3392.6; 3234.4; 3219.4; 1764.7 (β-lactam, νC=O); 1728.1; 1681.8; 1584.2, 1569.9 cm^{-1}.

MS (m/z): $[M-H]^-$ = 423.5.

^{1}H-NMR (DMSO-d6), δ (ppm): 3.68-3.86 (dd, 2H, -S-C**H**H-, J_1=9 Hz, J_2=25 Hz); 3.94 (s, 3H,-OCH_3); 4.95 (s, 2H, -C**H**$_2$O-); 5.21-5.23 (d, 1H, -C**H**-S-, *J*=5 Hz); 6.01-6.02 (d, 1H, -C**H**-CH-S, *J*=5 Hz); 6.62-6.63 (d,d 1H, -HC=C**H**-CH=, J_1=2 Hz, J_2=3.5 Hz); 6.67-6.68 (d, 1H, -**H**C=CH-CH=, *J*=5 Hz); 7.84-7.842 (d, 1H, -C**H**=CH-CH=,*J=2* Hz); 9.82 (s, 1H, -N**H**-).

4. Conclusions

Cefuroxime has been successfully prepared from 7-ACA and SMIA via the 4-step process, giving the total yield of Cefuroxime is 42%. This stage plays a main role for the next stages in the research and production of cephalosporin antibiotic materials in Vietnam. The novel feature of this study was the use of oxalyl chloride activating reagent. The process is good and green with the shorter time and the improved yield, the values are 1.5 hours and 90%, respectively. Moreover, the waste water only contains NH_4Cl, CO and CO_2 non-toxic compounds. The theme aims to find out the appropriate procedure for preparation of cefuroxime at the laboratory-scale in Vietnam.

5. Recommendations

This synthesis can be considered as a green process because the waste water only contained NH_4Cl, CO and CO_2 non-toxic compounds. And this process will be used for preparation of cefuroxime in Vietnam.

Acknowledgement

This research completed through the program supports basic scientific research of University of Natural Sciences HCMC.

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