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A NOVEL SYNTHESIS OF CEFIXIME FROM 7-AMINO-3-VINYL CEPHALOSPORANIC ACID (7-AVCA)

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ABSTRACT

The present invention relates to simple and easy process for the preparation of cefixime. 7-amino-3-vinyl cephalosporanic acid (7-AVCA) is reacted with 2-mercapto-1,3-benzothiazolyl-(Z)-2-(3-aminothiazol-4-yl)-2-(methoxy carbonyl)-methoxyimino acetate (MICE) in tetrahydrofuran and water mixture at 0-4^{o}C in the presence of triethanolamine. The novel feature of this study was the use of triethanolamine replaced triethylamine in the activation reaction between 7-AVCA with MICE. The results showed that, cefixime has high purity (HPLC purity: 97%) and total yield 66% in the reaction time of 1.5 hours (less than 30 minutes with previous process).

KEYWORDS: 7-AVCA; MICE; cefixime methyl ester; cefixime.

1. INTRODUCTION

Cefixime i.e., is a valuable semi-synthetic third-generation cephalosporin, which has antibiotic activity in the broad-spectrum of gram-positive and gram-negative microorganisms. Cefixime is a broad spectrum cephalosporin antibiotic and is commonly used to treat bacterial infections of the ear, urinary tract, and upper respiratory tract. It can be explained by the hydrolysis of esters in-vivo, therefore the absorption of cefixime in the gastro-intestinal increased. Cefixime was synthesized and marketed since the 1989s. There are numerous of publications on the synthesis of cefixime antibiotic.[2-7] US. Patent. No 2008/0242858 A1 and US. Patent. No 2010/7705142 B2 described the process for preparation of cefixime from 7-AVCA reacted with MICE in tetrahydrofurane and water mixture at the temperature in the range of 0-4^{o}C in the presence of triethylamine. The results showed that, cefixime has high purity (HPLC purity: 97%) and total yield 65% in the reaction time of 2.0 hours. However,

the waste solvent including hydrochloric acid, tetrahydrofurane, and ethyl acetate was toxic and the synthesis process was not green. CN 102079751A described method for preparation of cefixime trihydrate with cefixime side chain active ester and 7-AVCA. The total yield improved, but the activation reagent (TEA/DMF) was also not green.

In this study, we research on the preparation of cefixime from 7-AVCA and MICE in the presence of THF-water mixture in the activation of MICE [the activation reagent is triethanolamine] and the preparation of cefixime from cefixime methyl ester using sodium hydroxide. The study shows that the total yield of cefuroxime synthesized via the 2-step scheme is 66%. The process is good with the shorter time and the improved yield total, the values are 1.5 hours and 66%, respectively. The theme aims to find out the appropriate procedure for preparation of cefixime 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 triethanolamine (TEA, 99.5% purity, Thermo scienctific, India), Tetrahydrofurane (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 cefixime

We synthesis cefixim by a "one pot" process from two compounds 7-AVCA (1) and MICE (2). Preparation of cefixim based on the U.S. Patent 7,705,172 B2 by Bandi Parthasaradhi (2008, 2010)[2, 3] but some factors were adjusted through the steps in Scheme 1.

Step 1: Tetrahydrofuran (34 ml) is added to water (35 ml) and cooled to 4^{o}C, 7-AVCA (2,5 gm) and MICE (5,503 gm) are added at 4^{o}C. Then the mixture of triethanolamin (1,2 gm) and tetrahydrofuran (35 ml) is slowly added for 1 hours at 4^{o}C, stired for 4 hours at the same temperature. Then ethyl acetate (25 ml) is added. The contents are filtered through high-flow bed and washed the bed with ethyl acetate (10 ml). The aqueous layer is separated and

washed with ethyl acetate (35 ml) at 14^{o}C. The combined oganic layer is extracted with water (11 ml). Combine two layers of water, cool at 0°C and prepare the solution and crystallize in step 2.

Step 2: The water layer is cooled to 0°C, sodium hydroxide solution (1.35 gm NaOH in 75 ml of water) is added at once and stirred for 15 minutes at 0-8°C. Then 3 ml of 1:1 hydrochloric acid is added to the reaction mass at once to adjust to the pH to 4.8 to 5.2. Stirred for 30 minutes, then adjusted to the pH to 2.5 with 1: 1 Hydrochloric acid. The reaction mass is seeded with cefixime trihydrate, stirred for 30 minutes at 35^{o}C and cooled to 30^{o}C. Then the reaction mass is stirred for 3 hours at 30-32^{o}C, again cooled to 2^{o}C, and stirred for 30 minutes at 2-5^{o}C. The resulting solid is filtered, washed three times with chilled water (each time 10 ml) and dried to give 3.49 gm of white crystalline cefixime anhydrous.

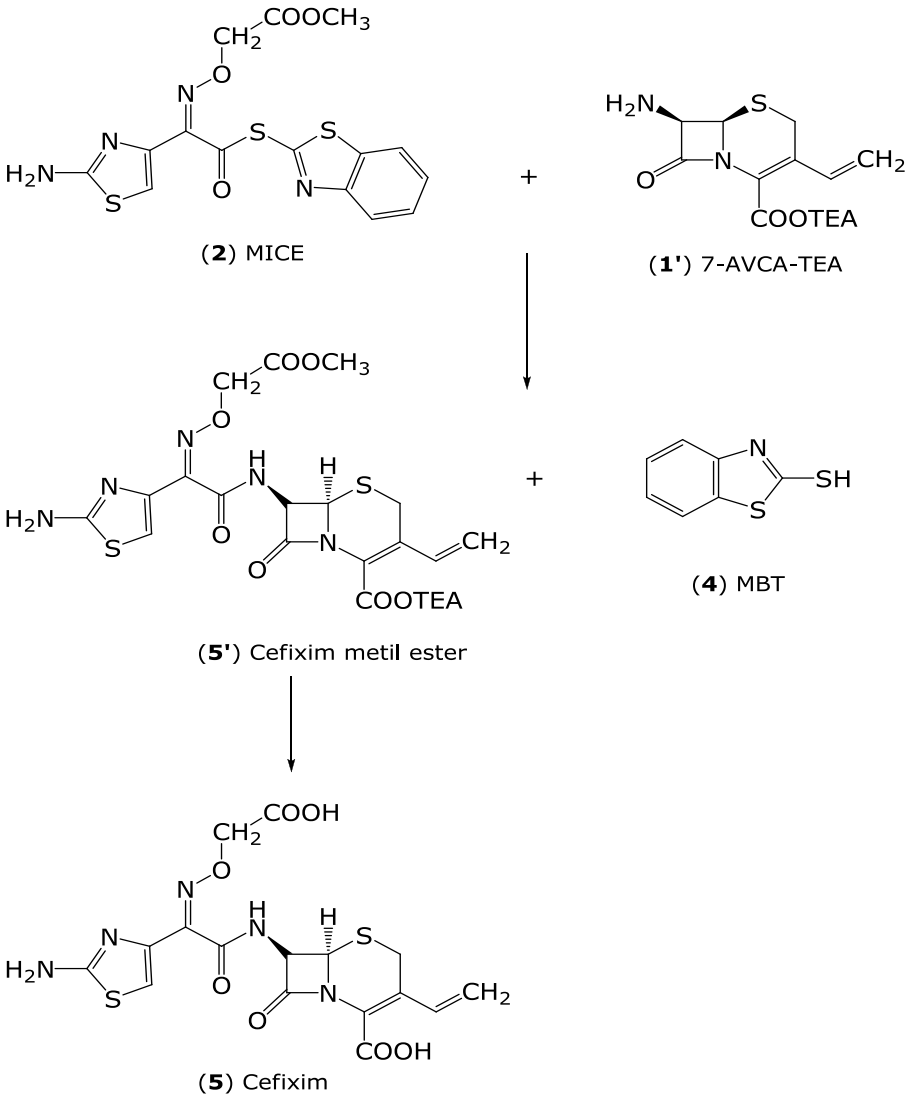

Diagram 1: The process for preparation of cefuroxime from 7-AVCA and MICE.

3. RESULTS AND DISCUSSION

The mechanism reaction of the preparation of cefixime is the ac-lattice-thymidine reaction between 7-AVCA and MICE, followed the reaction mass is hydrolyzed with sodium hydroxide solution to remove the -CH_3 group of cefixime methyl ester (5 ') and acidified with HCl (1: 1) get the product.

3.1. Spectral data used to determine cefixime product

The reaction product was determined as cefixim through HPLC/MS and NMR spectral data.

MS (m/z): $[M]^+$ (454), $[M + Na]^+$ (476).

^{1}H-NMR (DMSO-d6), δ (ppm): 3.58-3.61 (d, 1H, -S-CHH-, *J* = 15Hz); 3.84-3.87 (d, 1H, -S-CHH-, *J* = 15Hz); 4.60 (s, 2H, -O-CH_2-); 5.21-5.22 (d, 1H, -CH-S-, *J* = 5Hz); 5.32-5.34 (d, 1H, -C = CHH, *J* = 12Hz); 5.59-5.62 (d, 1H, -C = CHH, *J* = 15Hz); 5.81-5.83 (dd, 1H, -CH-CH-S-, J_1 = 4.5Hz, J_2 = 9Hz); 6.82 (s, 1H, -S-CH =); 6.90-6.95 (dd, 1H, -CH = CH_2, J_1 = 4.5Hz, J_2 = 15Hz); 7.26 (s, 2H, -NH_2); 9.55-9.56 (d, 1H, -C (= O) -NH-, *J* = 9Hz).

^{13}C-NMR (DMSO-d6), δ (ppm): 23.30 (S-CH_2 -); 57.56 (-CH-CH-S); 58.80 (-CH-CH-S); 70.44 (-O-CH_2-); 110.27 (-S-CH =); 117.29 (-CH = CH_2-); 124.44 (N-C (= C) -COOH); 125.3 (-CH_2-C-); 131.82 (-C = CH_2); 141.95 (S-CH = C-N); 149.77 (H_2N-C-); 162,32 (-N-C = O); 163.06 (N-C (= C) -COOH); 163.46 (-NH-C = O); 168.39 (-C = N-); 170.96 (-CH_2-COOH).

3.2. The survey molar ratio of 7-AVCA : MICE in the reaction

During the study, we kept the reaction conditions such as reaction temperature, crystallization temperature, Triethanolamin content (TEA), NaOH content, ... according to U.S. Patent 7,705,172 B2 and only change the mole ratio between 7-AVCA: MICE. Obtain the following results.

Table 1: The survey molar ratio of 7-AVCA : MICE in the reaction.

The molar ratio 7-AVCA : MICE	The HPLC purity (%)	The weight (g)	The Yield (%)
1 : 1,1	77	3,11	48
1 : 1,2	**92,5**	**3,49**	**66**
1 : 1,5	62,5	3,65	46
1 : 2,0	56	3,92	44

Comment

The yield of reaction is relatively good. When the molar ratio of 7-AVCA: MICE increased, the content of MICE in the product increased. Based on this table, it was found that with the molar ratio of 7-AVCA: MICE = 1: 1,2, the product obtained the highest purity of 93% and the yield reaction is 66% (compared to the author of US Patent 7,705,172 B2 is 71%) but time reaction is less than 0.5 hours (compared to US Patent 7,705,172 B2).

Refined the cefixime: We refined cefixime to obtained cefixime purity, corresponding to a sample cefixime 92.5% purity, obtained higher purity cefixime and reached the Vietnamese Pharmacopoeia Standard IV (DĐVN IV). Refining diagram:

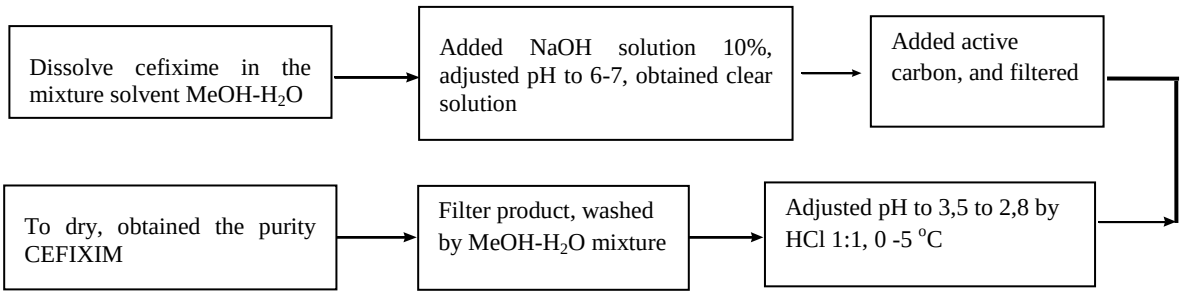

Diagram 2: Diagram refining cefixime.

The product after the refining, was tested by HPLC with a purity of 97% HPLC. And test the important physical properties such as rotation power, pH, water content (according to Vietnamese Pharmacopoeia Standard IV) and results as follows:

Table 2: Some physical indicators of cefixim samples after refining.

Physical property	Analysis method	Value	Standard value	Result
Shape		White and yellow powder		Compatible
Rotation power	DĐVN IV	-82^{o}	-75^{o} to -88^{o}	OK
pH	DĐVN IV	3,5	2,6-4,1	OK
Water content	DĐVN IV	11,2%	9-12%	OK

The comment: In general, cefixim product have reached the standards about pH, rotation power, water content, as well as the purity HPLC according to Vietnamese Pharmacopoeia Standard IV. So this process into trial production as well as the practical application of this production process in the pharmaceutical industry is possible.

4. CONCLUSIONS

Cefixime is a third generation cephalosporin antibiotic, was prepared from the 7-AVCA and MICE in the presence of THF-water mixture in the activation of MICE [the activation reagent is triethanolamine] and the preparation of cefixime from cefixime methyl ester using sodium hydroxide. Based on the selection method, cefixime was purified at 97% purity HPLC, reaching pH standards, rotation power, water content according to the Vietnamese Pharmacopoeia Standard IV. The study shows that the total yield of cefuroxime synthesized via the 2-step scheme is 66%. The process is good with the shorter time and the improved yield total, the values are 1.5 hours and 66%, respectively. The theme aims to find out the appropriate procedure for preparation of cefixime at the laboratory-scale in Vietnam.

5. Recommendations

This synthesis process provides a simple and effective method for the production of cefixime antibiotic, raw materials antibiotic in Vietnam.

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