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NOTE

Synthesis of Cefdinir from 7-Amino-3-vinyl Cephem-4-carboxylic Acid Using N-Methyl Morpholine as Base

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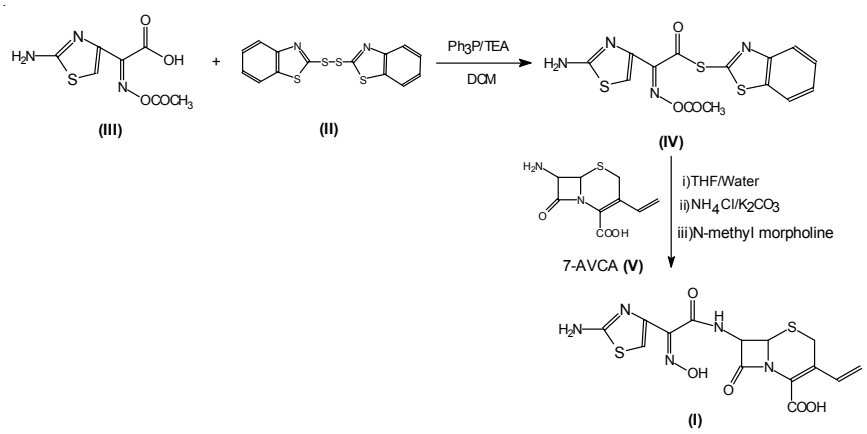
In this paper, synthesis of cefdinir (**I**) from 7-amino-3-vinyl cephem-4-carboxylic acid (**V**) is reported by reacting with 2-mercapto benzothiazolyl (Z)-2-(2-amino-4-thiazolyl)-2-acetoxyimino acetate (**IV**) in presence of base, N-methyl morpholine.

Key Words: Cefdinir, N-methyl morpholine, Synthesis.

Cefdinir (**I**), 7β-[(Z)-2(2-amino-4-thiazolyl)-2-hydroxyimino acetamido]-3-vinyl cephem-4-carboxylic acid is an orally effective, third generation, semi-synthetic cephalosporin with an extended antibacterial spectrum[1-3]. Several synthetic approaches have been reported for the preparation of cefdinir[4-8] and these methods comprise of certain disadvantages which include long reaction time, poor yield, use of large volume of solvents and inferior quality of finished product. Herein, a convenient synthesis of cefdinir from 7-amino-3-vinyl cephem-4-carboxylic acid (7-AVCA) employing 2-mercapto benzothiazolyl (Z)-2-(2-amino-4-thiazolyl)-2-acetoxyimino acetate (**IV**) and using the base N-methyl morpholine at ambient temperature is reported (**Scheme-I**).

Preparation of 2-mercapto benzothiazolyl (Z)-2-(2-amino-4-thiazol)-2-acetoxy imino acetate (IV): A mixture of anhydrous (Z)-2-(2-amino-4-thiazol)-2- acetoxy iminoacetic acid (**III**, 164 g, 0.716 mol), triphenyl phosphine (235.5g, 0.899 mol) and *bis*(benzothiazol-2-yl) disulphide (**II**, 249.8 g, 0.752 mol) were taken in MDC (2460 mL) and stirred for 0.5 h at 15-20 °C. Thereafter, triethylamine (76.09 g, 0.753 mL) was added gradually at the same temperature and stirred for another 0.5 h. The reaction was monitored by HPLC. On completion of reaction the precipitated product was filtered and washed with methylene chloride (656 mL) and dried under vacuum to afford (**IV**) as a yellow product (165 g, 80 %).

Preparation of 7β-[(Z)-2(2-amino-4-thiazolyl)-2-hydroxyimino acetamido]-3-vinyl cephem-4-carboxylic acid (I, cefdinir): A mixture of 7-amino-3-vinyl cephem-4-carboxylic acid (**V**), (216.5 g, 0.957 mol)



Scheme-I

compound (**IV**) (354.5 g, 0.938 mol) were taken in aqueous THF (866 mL of water and 2165 mL of THF) at ambient temperature and stirred for 15 min. Thereafter, N-methyl morpholine (1.05 mol) added over 10 min at the same temperature. After complete addition, the reaction mixture was stirred for another 3 h at 25 to 30 °C. The reaction was monitored by HPLC. When unreacted staring material **V** was less than 1 %, it was extracted with methylene chloride (1082 mL × 3) to remove mercapto benzothiazol and THF followed by the addition of water (866 mL). Thereafter, the aqueous layer was degassed under reduced pressure at 25-30 °C to remove the traces of dichloro methane. Then ammonium chloride (143.4 g, 2.63 mol) was added to the aqueous layer and subsequent hydrolysis was carried out by adding potassium carbonate solution (173.1, 20 % v/v, 865.5 mL) while maintaining the pH between 8 to 8.2 at 15 to 20 °C. The reaction was monitored by HPLC. On completion of hydrolysis reaction, the pH was brought upto 2.5 to 2.8 by adding H_2SO_4 at 25 to 30 °C and stirred for another 45 min to complete precipitation. The solid was filtered and wash with cold water to afford semi pure cefdinir as an off white powder. The product was purified as per the available literature as follows[9,10]. Trifluoroacetic acid (359.2 g) was added to a stirred suspension of semi pure cefdinir and water (3234 mL) at 35 to 35 °C in 0.5 h. Then it was cooled to 5-10 °C and stirred for another 45 min to complete precipitation. The solid was filtered and washed with cold water to afford wet cefdinir TFA salt. The wet cefdinir TFA salt was suspended in water and pH was adjusted to 6.5 to get the clear solution with 10 % w/w aqueous ammonia (220.5 mL) solution at 15-20 °C. Carbon (5 %) was added and the suspension was stirred for 0.5 h at the same temperature. Carbon was filtered and washed with water. Aqueous HCl (10 % v/v, 225 mL) was added to the filtrate at 10 to 15 °C to adjust pH to 2.5 to 2.8 in

0.5 h. The precipitated product was stirred for another 45 min at the same temperature to complete the precipitation. The solid was filtered and washed with cold water (0-5 °C). The wet material dried at 40-45 °C to afford compound **1** (336 g, 85 %).

Water (% w/w, by KF); 6.0-7.5; IR (KBr, ν_{max}, cm^{-1}) 3302, 3176 (NH), 1784 (β-lactam CO), 1668 (amide CO), 1611 and 1429 (acid CO), 1350 and 1334 (NH_2), ^1H NMR (DMSO) δ 3.53 and 3.82 (ABq, 2H, *J* = 17.6 Hz), 5.19 (d, 1H, *J* = 4.8 Hz), 5.33 (d, 1H, *J* = 11.2 Hz), 5.61 (d, 1H, *J* = 17.6 Hz), 5.79 (m, 1H), 6.67 (s, 1H), 6.91 (dd, 1H, *J* = 11.2 Hz and 17.6 Hz), 7.16 (bs, 2H), 9.50 (d, 1H, *J* = 8.0 Hz), 11.32 (s, 1H) 13.62 (brs, 1H); MS: m/z 395 (M^+).

In an attempt to investigate the influence of base, the condensation of 7-AVCA (**V**) and the compound **IV** was similarly carried out in presence of other bases such as, morpholine, N-methyl pyrrolidone, pyridine at ambient temperature necessitated longer reaction time (6 to 10 h) and led to comparatively lower yields of product (55-60 %). In literature, alkyl amine particularly triethyl amine is used in the reaction but use of N-methyl morpholine is not mentioned for the same reaction. The use of N-methyl morpholine gave slight improvement in the yield of the product (85 %) and also the reaction progresses smoothly. It was presumed and probably due to the presence of nitrogen atom in the ring system it acts as a mild base and reaction completes effectively. However, when the reaction of **IV** and **V** was carried out without base, the desired product is failed to obtained. It is found that reaction takes place efficiently when N-methyl morpholine was used as base.

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