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An improved and scaleable preparation of Cefradine

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Abstract: Cefradine (I) is prepared from 7-amino desacetoxy cephalosporanic acid (7-ADCA) (II) condensing with mixed anhydride that is obtained from reaction of dihydrophenylglycine methyl dane sodium salt (IV) with pivaloyl chloride in presence of triethyl amine.

Keywords: Antibiotics, Cefradine, 7-Amino desacetoxy cephalosporanic acid, Pivaloyl chloride, Dihydrophenylglycine methyl dane sodium salt

Introduction

Cephalosporin-type antibiotics were first isolated in 1961 from the extract of *cephalosporium acremonium*[1] and are based on 7-aminocephalosporanic acid[2]. Cephalosporins are semisynthetic antibiotics which are widely used in medicine and are similar in structure and mechanism of action to penicillins[3]. Cefradine (7-[a-D-(cyclohexa-1,4-dienyl)-glycyl-amino]-3-methyl-3-cephem-4-carboxylic acid) is a first-generation cephalosporin, originally isolated in 1948[4,6]. There are several synthetic methods reported for the preparation of cefradine[5-11]. There is still a need for a general, mild and inexpensive approach for the synthesis of cefradine. In present work, cefradine is prepared from 7-amino desacetoxy cephalosporanic acid (7-ADCA) and is confirmed by spectra analysis.

Results and discussion

In the present paper, we report an improved and scalable process with respect to improvement of yield and product quality, use of less expensive raw materials and lower consumption of solvents. In this improved process, 7-ADCA reacted with bistrimethylsilylurea in toluene to give silylated 7-ADCA (III). The resulting (III) is then reacted with mixed anhydride (V) that is obtained from the reaction of dihydrophenylglycine methyl dane sodium salt with mixed anhydride (V) that is obtained from the reaction of dihydrophenylglycine methyl dane sodium salt with pivaloyl chloride in presence of triethylamine (TEA) in dichloromethane to give cefradine. During the process optimization, we paid great attention to operation simplicity on a commercial scale. For silylation of 7-ADCA, we have studied the effect of bistrimethylsilylurea in comparison to a mixture of hexamethyl disilazone (HMDS) and trimethyl chlorosilane in 1: 0.3 molar ratio. Using bistrimethylsilylurea causes higher yield (96%) than the yield of the other silylated reagents (75%). Similarly the effects of triethylamine and N-methyl morpholine, during the reaction have been studied. For higher conversion, triethylamine was better base.

Conclusion

Cefradine (I) can be prepared in excellent yield and high purity by reaction of silylated 7-ADCA (III) with mixed anhydride (V) that is obtained from the reaction of dihydrophenylglycine methyl dane sodium salt (IV) with pivaloyl chloride in presence of triethylamine (TEA). Process for synthesis of cefradine is useful for a pharmacist to synthesis cephalosporin drugs.

Experimental

7-amino desacetoxy cephalosporanic acid (7-ADCA) (II) is silylated with bistrimethylsilylurea in dichloromethane. Bistrimethylsilylurea (BSU) is prepared from urea with hexamethyl disilazone

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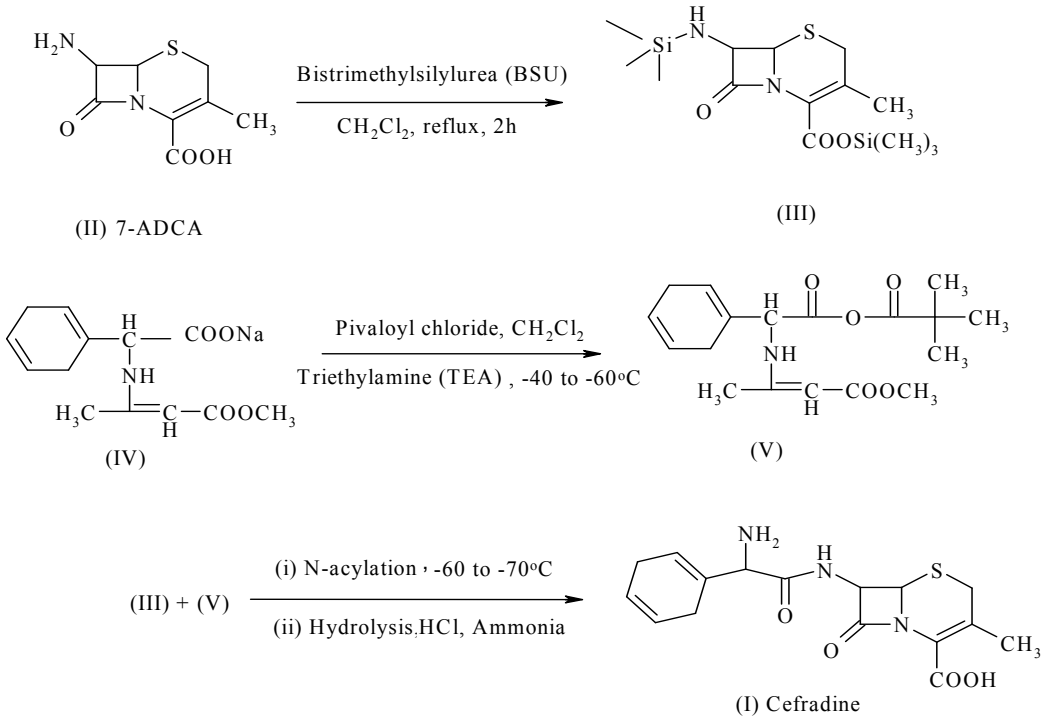
(HMDS) in presence of trimethyl chlorosilane (TMCS) in toluene. In parallel, mixed anhydride (V) is prepared from dihydrophenylglycine methyl dane sodium salt (IV) with pivaloyl chloride in presence of triethylamine (TEA) in dichloromethane. Then, N-acylation of silylated 7-amino desacetoxy cephalosporanic acid with mixed anhydride (V) was carried out at -60 to -70°C. After completion of the reaction, it was di-silylated by acidic water and extracted desired product in aqueous layer. The pure compound (I) was isolated at pH 5.0 by addition of dilute ammonia solution (Scheme-1).



Scheme 1: Synthesis of Cefradine

In a dry reaction vessel for preparation of BSU, 2 L TMCS and 42 L HMDS was added to 11 kg urea in 120 L toluene and refluxed for 3.5 h. Then 100 kg 7-ADCA was added to prepared bistrimethylsilylurea (BSU) in 350 L dichloromethane and refluxed for 2h. Separately, 75 kg pivaloyl chloride was added to a mixture of 175 kg dihydrophenylglycine methyl dane sodium salt (IV), 115 L triethylamine in 400 L dichloromethane at 38°C for 30 min, stirred for 3h at -40 to -60°C. Silylated mixture (III) was added to mixed anhydride (V) at -60 to -70°C till HPLC analysis shown less than 1% of 7-ADCA. After completion of the reaction, the above solution was quenched with 235 L water and pH (3.0) adjusted by conc. HCl solution. The resulting mixture was again stirred and then allowed to separate. Aqueous layer was extracted with dichloromethane twice (each 140 L), pH (5.0) of aqueous layer was adjusted slowly by dilute ammonia solution to precipitate compound (I). The crude product was filtered and washed with cooled water and dried at 50°C to yield cefradine (150.8 kg, HPLC purity: 95%). The crude product was purified by dissolving in dilute HCl at pH 3.0 and subjected to carbon treatment, filtered and was re-precipitated by ammonia solution at pH 5.0. The cake was washed with cooled water and dried at 50°C under reduced pressure to yield pure cefradine (146 kg, HPLC purity> 99%).

Spectral data [cefradine (I)]: IR spectra (in KBr): 1780 cm^{-1}, 1690 cm^{-1} and 1560 cm^{-1}, ^{1}H-NMR (DMSO-d_6, 400MHz): 1.81 (CH_3, S), 2.4-2.7 (2(=C-CH_2-C=), m), 3.1 (N-CH-C, d, j=4.2), 3.21 (CH_2^a-S, d, j=17), 3.33 (CH_2^b-S, d, j=17), 3.51 (N-CH-Cyclo, S), 3.85 (N-CH-S, d, j=4.2), 4.70 (NH_2, S), 5.1-6.4 (-CH=CH-, m), 8.3 (NH-C=O,S), 10.8 (COOH, S), Mass spectra: 349 m/z.

Spectral data [silylated mixture (III)]: IR spectra (in KBr): 1775 cm^{-1}, and 1660 cm^{-1}, ^{1}H-NMR (DMSO-d_6, 400MHz): 0.62 (N-Si$(CH_3)_3$, S), 0.85 (O-Si$(CH_3)_3$, S), 1.80 (CH_3, S), 3.1 (N-CH-C, d, j=4.2), 3.18 (CH_2^a-S, d, j=17), 3.29 (CH_2^b-S, d, j=17), 3.83 (N-CH-S, d, j=4.2), 4.1 (NH, S), Mass spectra: 345 m/z.

Spectral data [mixed anhydride (V)]: IR spectra (in KBr): 1820 cm^{-1}, 1710 $cm^{-1}$and 1685 cm^{-1}, ^{1}H-NMR (DMSO-d_6, 400MHz): 1.21 ($C(CH_3)_3$, S), 1.95 (CH_3, S), 2.4-2.7 (2(=C-CH_2-C=), m), 3.64 (CH-N, S), 3.91 (O-CH_3, S), 4.58 (NH, S), 6.21 (C=CH-C=O, S), 5.1-6.4 (-CH=CH-, m), Mass spectra: 324m/z.

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References

[1] Abraham, E. P.; Newton, G. G. F. *Biochem. J.* **1961**, *79*, 377.

[2] Serkov, I. V.; Bezuglov, V. V. *Chem. Nat. Comp.* **2007,** *43***,** 103.

[3] Beger, R. *Drug Discov. Today,* **2006**, *11***,** 429.

[4] Joseph, E. D.; Harold, E. A. *J. Med. Chem.* **1971**, *14*, 117.

[5] Sultana, N.; Saeed Arayne, M.; Afzal, M. *Pak. J. Pharm. Sci.* **2005**, *18*, 36.

[6] Lei, D.; Wenbo, L.; *The Open Catalysis J*. **2010,** *3*, 19.

[7] Robinson, C. A. *U.S. Pat*. US 3965098, **1976**.

[8] Diago, J.; Ludescher, J. *U.S. Pat*., US 5719276, **1998**.

[9] Heemskerk, D.; Hogenboom, A.; Lenhardt, C.; Moody, H.; Dooren, T. *U.S. Pat*., US 0189802 A1, **2002**.

[10] Broggi, R.; Falciani, M. *U.S. Pat*., US 4139702, **1979**.

[11] Kemperman, G. J.; Zhu, J.; Klunder, A. J. H.; Zwanenburg, B. *Eur. J. Org. Chem.* **2001**, *10*, 1817.