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Commercial Synthesis of Cefprozil: Development and Control of Process Impurity[†]

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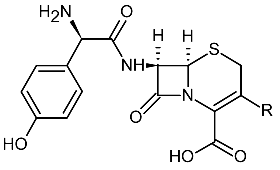
ABSTRACT: A process impurity, ethoxycarbonylcefprozil (**9**), formed in the synthesis of cefprozil (**1**) was controlled with addition of a catalytic amount of methanesulfonic acid.

INTRODUCTION

Cephalosporins are an important class of β-lactam antibiotics. Cefprozil (**1**), cefadroxil (**2**), and cefatrizine (**3**) antibiotics have a common side chain, namely *p*-hydroxy phenyl glycine. Cefprozil, developed by Bristol-Myers-Squibb, is an effective broad spectrum antibiotic useful in the treatment of respiratory tract, ear, and skin infections, etc.[1] It is a mixture of *Z* and *E* isomers, with *Z* primarily responsible for the antibiotic activity.[2] The synthetic process[3] for the commercial production involves condensation of the acid chloride of *p*-hydroxy phenyl glycine or mixed anhydride of Dane salt **6** with 7-amino-3-(propen-1-yl)-3-cephem-4-carboxylic acid (7-APCA, **4**) (Scheme 1). The Dane salt route was preferred over the amino acid chloride route due to the commercial availability of Dane salt **7**, better yield, and poor stability of acid chloride.[4]



R	
-CH=CH-CH_3	Cefprozil (**1**)
-Me	Cefadroxil (**2**)
-CH_2-S-Triazine	Cefatrizine (**3**)

The ICH guidelines require all the process impurities to be controlled either through the starting materials, isolated intermediates or in the API. In the API all the known impurities need to be controlled with a limit of not more than 0.15%.[5] This article reports the control of a process impurity ethoxycarbonylcefprozil (**9**), which is formed during the reaction.

RESULTS AND DISCUSSION

Our methodology to manufacture cefprozil involves condensation of silylated 7-APCA **5** with the mixed anhydride of Dane salt **7** (Scheme 1). The limit for *E* isomer content in API as per U.S. Pharmacopoeia is 8−11%, which is controlled through starting material 7-APCA (**4**). A method to achieve the desired ratio is disclosed in our earlier publication.[6] The manufacturing process for cefprozil involves formation of a mixed anhydride of Dane salt (**7**) by the reaction of **6** with ethyl chloroformate in the presence of catalytic amount of *N*-methyl morpholine (NMM). NMM catalyzed the mixed anhydride formation to get complete conversion.[4] This is then condensed with silylated 7-APCA **5**. The analysis showed an impurity ethoxycarbonylcefprozil (**9**) in API in the range 0.3−0.8%. Attempted purification of API did not give the desired result; hence, there was a need to control this impurity. Our emphasis was to investigate the root cause and control its formation during the reaction. The HPLC monitoring showed the impurity in the reaction mixture with a range from 0.5 to 1.25%. Our studies revealed that this impurity is generated during the mixed anhydride formation of **6**. The formation of impurity is possible by the reaction of phenolic OH with ethyl chloroformate under the given conditions (Scheme 2). Experiments were carried out to minimize this impurity formation during reaction. It was found that the addition of a catalytic amount of an organic acid along with a catalytic amount of NMM reduced the formation of this impurity drastically. Different organic acids were tried, and results are tabulated in Table 1.

Among the various organic acids tried, such as acetic acid, formic acid, 3-(*N*-morpholino)propanesulfonic acid (MOPS), and methanesulfonic acid (MSA), the best result was obtained with MSA. MOPS did not have any impact in reduction of impurity. In a typical experiment, MSA (5 mol %) and NMM (2 mol %) were added to Dane salt **6** and treated with ethyl chloroformate. The mixed anhydride **7** thus formed is condensed with silylated 7-APCA **5**, and product is isolated as DMF solvate. Cefprozil regenerated as monohydrate by desolvation of DMF solvate in water with 77% yield and impurity **9** in the range of 0.04−0.07%.

CONCLUSION

We have effectively controlled the formation of ethoxycarbonyl impurity **9** during the reaction with the use of a catalytic amount of methanesulfonic acid. With this improvement, high quality cefprozil is manufactured.

EXPERIMENTAL SECTION

General. Reagents were used as such without purification. ^1H NMR (400 MHz) spectra was recorded using a Bruker spectrometer. The chemical shift data is reported as δ (ppm) using tetramethylsilane as internal standard. Mass spectrum was recorded using an API 2000 (MPS SCIEX) instrument. Infrared spectrum was recorded using PerkinElmer FTIR (Spectrum One) instrument. HPLC analysis was performed on a Waters/Agilent instrument with a UV detector (220 nm) using Inertsil ODS-3 V (250 mm × 4.6 mm, 5 μm) column. Column oven temperature: 30 °C, Sample tray temperature: 4 °C Mobile phase

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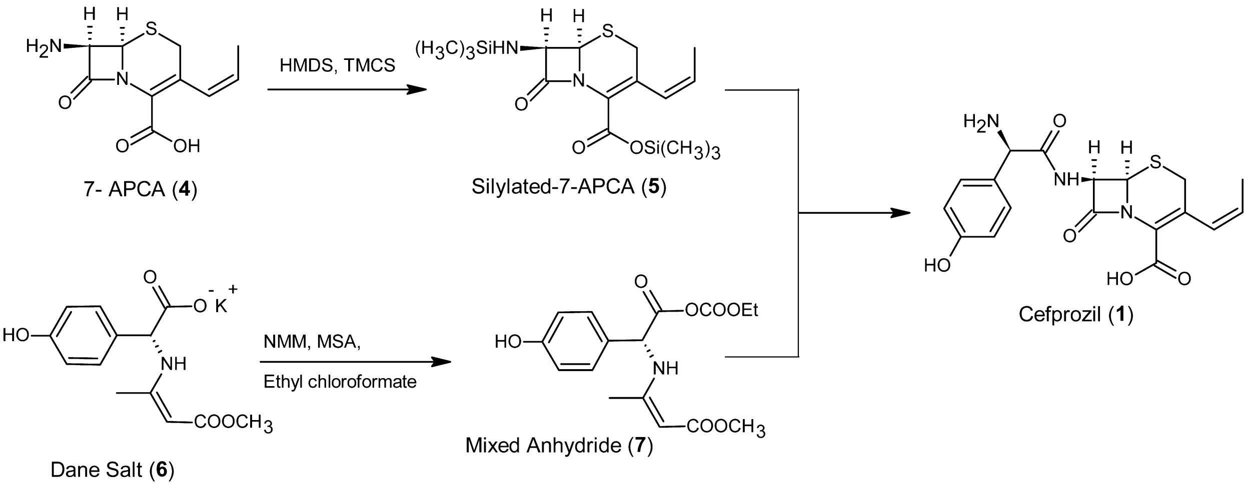
Scheme 1. Formation of Cefprozil



Scheme 2. Impurity Formation Pathway

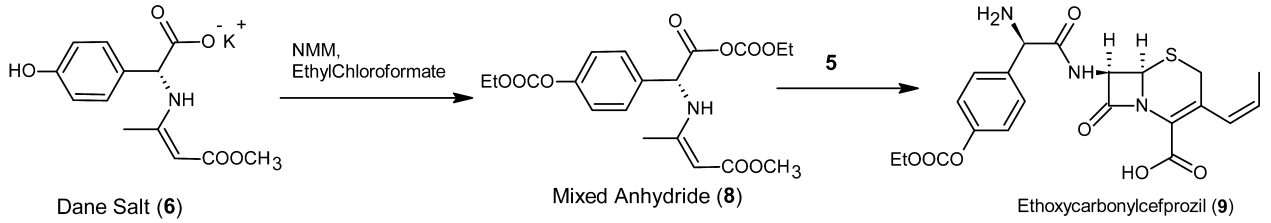


Table 1. Effect of Acid in the Formation of 9

organic acid	impurity 9[a] Z/E (%)	impurity in API 9 Z/E (%)
-	1.19/0.13	0.65/0.09
-	0.66/0.1	0.34/0.13
Acetic acid	0.14/0.02	0.12/ND
MOPS	1.31/0.26	Not tested
Formic acid	0.09/0.01	0.1/ND
Methanesulfonic acid	0.07/0.01	0.04/ND

[a] HPLC reaction monitoring, ND = not detected.

A [Aqueous Monobasic sodium phosphate (0.04% *w/w* solution) adjusted pH to 4 ± 0.05 with dilute *ortho* phosphoric acid]: Mobile phase B [mixture of mobile phase A and acetonitrile 50:50 *v/v*], flow rate: 1.0 mL/min, gradient 95:5 (0−20 min), 70:30 (20−40 min), 40:60 (40−50 min), 0:100 (50−62 min), 95:05 (60−70 min)

*Preparation of Cefprozil (**1**). Part A: Silylation of 7-Amino-3-(propen-1-yl)-3-cephem-4-carboxylic acid (7-APCA).* 7-APCA (**5**, 120 kg, 0.5 kmol) was added to methylene chloride (420 L) followed by 1,1,3,3-hexamethylsilazane (60.36 kg, 0.375 kmol), chlorotrimethyl silane (42.25 kg, 0.39 kmol) and imidazole (1.2 kg). The reaction mixture was then refluxed for 3−4 h and cooled to 0−5 °C.

*Part B: Mixed Anhydride Formation **7**.* Potassium (D)-*N*-(1-methoxycarbonyl-propen-2-yl-α-amino-*p*-hydroxy phenyl acetate (Dane Salt, **6**, 168.8 kg, 0.56 kmol) was added to methylene chloride (720 L) and DMF (540 L) and stirred at −40 − −45 °C. *N*- Methyl morpholine (1 kg, 2 mol %) and methanesulfonic acid (2.4 kg, 5 mol %) were added followed by ethyl chloroformate (67.68 kg, 0.62 kmol) and stirred for about 2 h at −38 to −48 °C. Then cooled to −60 to −65 °C

Part C: Condensation and Isolation of Cefprozil DMF Solvate. The solution of silylated 7-APCA (part A) was added to part B, mixed anhydride keeping the temperature below −40 °C over a period of 10−15 min. After the addition, the mixture was stirred for 1 h at −40 − −45 °C. Then the temperature was raised to −30 °C and the reaction monitored by HPLC. The reaction mixture was added to a mixture of conc. HCl and water (84 and 410 L), stirred for 15 min at 0−5 °C and separated the aqueous layer. The aqueous layer then diluted with DMF (1200 L) and acetone (360 L) at 0−10 °C. Activated carbon (12 kg) was added, stirred for 15−20 min at 0−10 °C. The resulting mixture was filtered, washed with DMF (600 L) and the pH of the filtrate was adjusted to 5.0−5.5 using aqueous ammonia (25%) at 15−20 °C. This solution was seeded with cefprozil DMF solvate (0.250 kg) and stirred for 15- 20 min. Then the pH was adjusted to 6.4−6.5 with aqueous ammonia and stirred for 1 h at 15−20 °C. The product was filtered, washed with DMF (240 L) followed by acetone (2 × 1200 L) and dried at 30−35 °C for 12−14 h under vacuum to give DMF solvate in 88% yield (203 kg).

*Part D: Preparation of Cefprozil Monohydrate (**1**).* Cefprozil DMF solvate (203 kg) from part C was added to water (825 L) at 30−35 °C in 40−60 min and stirred for 1.5 h. The slurry was then cooled to 0−5 °C and stirred for 2 h. The product was filtered and washed with chilled water (120 L) and acetone (2 × 300 L). The wet material was dried under vacuum at 40−45 °C until water content is 4−5% (*w/w*) to give cefprozil monohydrate (158 kg) in 77% yield. HPLC Purity: 99.47%, Ethoxycarbonyl impurity: 0.07%, MS: $m/z = 390$ $[M + H]^+$; IR (KBr) (cm^{-1}): 1762, 1681, 1560. ^1H NMR (400 MHz, CF_3COOD): 8.17−8.2 (d, 2 H), 7.78−7.81 (d, 2 H), 6.94−6.98 (d, 1 H), 6.61−6.68 (m, 1 H), 6.45−6.46 (d, 1 H), 6.18 (d, 1 H), 5.94−5.95 (d, 1 H), 4.05−4.24 (q, 2H), 2.39−2.41 (d, 3H).

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Author Contributions

[†]A patent application incorporating parts of this report has been filed.

Notes

The authors declare no competing financial interest.

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