Organic Process Research & Development **2003**, *7*, 758−761

Identification and Control of a Process-Related Impurity in the Chlorination of 3-Hydroxy-3-carbacephem

Yatendra Kumar,* Neera Tewari, Hashim Nizar, Bishwa Prakash Rai, and Shailendra Kumar Singh

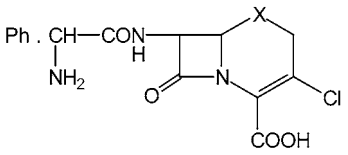
Chemical Research Division, Ranbaxy Research Laboratories, Gurgaon, Haryana - 122 001, India

Abstract:

A process for the synthesis of carbacephem key intermediate (4-nitrophenyl)methyl,7-amino-1-carba(dethia)-3-chloro-3-cephem-4-carboxylate, monohydrochloride (1) via chlorination and deacylation employing chlorotriphenoxyphosphonium chloride [$(PhO)_3P^+ClCl^-$] has been described. The most difficult problem encountered during the process development was the formation of an impurity 2, which has been isolated, identified, and controlled by modifying the reaction conditions.

Introduction

Loracarbef **(3a)** is the first carbacephem antibiotic, an analogue of the most widely used cephalosporin antibiotic cefaclor **(3b)**. It is an orally active broad-spectrum antibiotic used in the treatment of infections of the respiratory system and urinary tract and for skin infections.[1]



3 a, X = CH_2, Loracarbef
b, X = S, Cefaclor

The carbacephems have been prepared by total synthesis in contrast to cephalosporin antibiotics.[1] Since these are obtained by total synthesis, purity of the intermediates involved plays an important role in the formation of the final drug molecule. The conversion of (4-nitrophenyl)methyl, 7-phenoxyacetamido-1-carba(dethia)-3-hydroxy-3-cephem-4-carboxylate **(4)** to intermediate **1** is the key step in the total synthesis of loracarbef. Different synthetic methods are reported in the literature for the above conversion.[2] In the preparation of intermediate **1**, our strategy involves deacylation and chlorination in single step, utilizing Hatfield reagent.[2b,c] This reagent is prepared by the reaction of triphenyl phosphite with chlorine gas, resulting in the formation of chlorotriphenoxyphosphonium chloride [$(PhO)_3P^+ClCl^-$]. During the attempted two-step chlorination and deacylation using this reagent,[2b,c] only N-deacylation is reported.[2a] However, another publication mentions the deacylation and chlorination in a single step using the above reagent.[2d] J. E. Burks et al.[2e] have studied the kinetic differences in the chlorination of cephalosporins vs that of carbacephems with this reagent and report that chlorination of carbacephems requires higher temperatures compared to that of cephalosporins. With our prior practical experience with cephalosporin molecules using the Hatfield reagent, we observed that carbacephem behaves differently and faced problems in the preparation of pure intermediate **1**. In this report, we highlight the issues encountered during the process development and describe a scalable process for synthesis of intermediate **1** from intermediate **4**.

Results and Discussion

The intermediate **1** is prepared by the reaction of intermediate **4** with chlorotriphenoxy phosphonium chloride in the presence of pyridine in a mixture of ethyl acetate and dichloromethane. Scheme 1 outlines the reaction pathway for the conversion of enol **4** to the chloro intermediate **1** using chlorination reagent $(PhO)_3P^+ClCl^-$ which involves rapid, reversible chloride addition to an intermediate enol phosphonium species followed by rate-limiting phosphate departure.[2e]

It is observed during our development work that an impurity at the level of 20−25% is formed and present in the isolated product in 15−20% (as determined by HPLC), which resulted in inferior yield and quality of intermediate **1**. The above impurity is isolated and characterized by different spectroscopic data and is assigned the structure as **2**, which shows a pyridyl substitution at the 3-position instead of chlorine. The impurity **2** is formed by the attack of pyridine instead of chloride ion in the above phosphonium species **5**. There is no literature report for a similar nucleophilic attack of pyridine and formation of impurity **2.** The proposed mechanism is shown in Scheme 2.

* Author for correspondence. E-mail: yatendra.kumar@ranbaxy.com. Telephone (91-124) 234 2020. Fax (91-124) 501 1832.

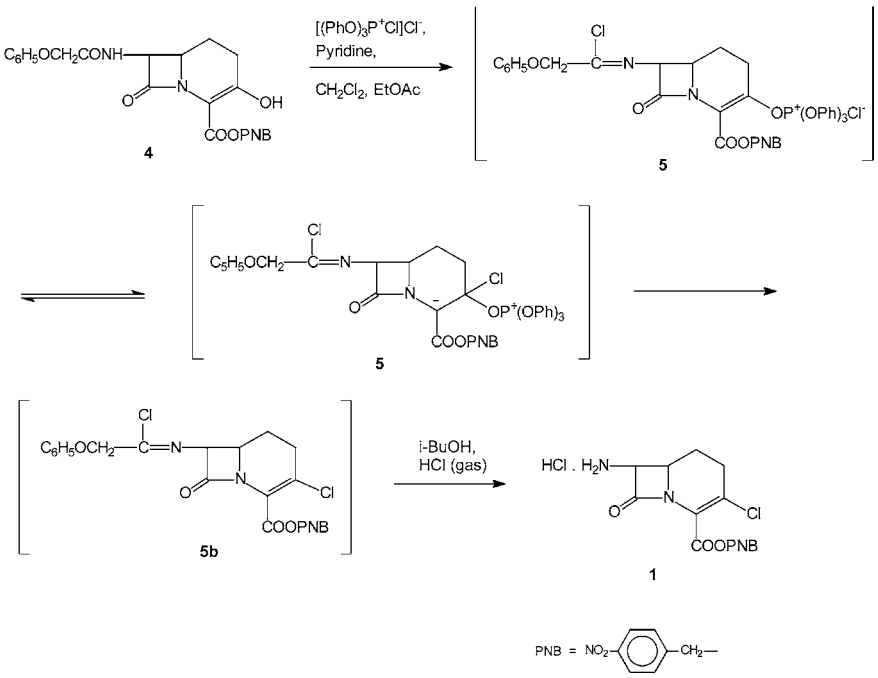
(1) (a) Kant, J.; Walker, D. G. In *The Organic Chemistry of β-Lactams*; Georg. G. I., Ed.; VCH: New York, 1993; pp 121−196. (b) Metais, E.; Overman, L. E.; Rodriguez, M. I.; Stearns, B. A. *J. Org. Chem.* **1997**, *62*, 9210.

(2) (a) Bodurow, C. C. (Eli Lilly). E.P. Patent 348,124, 1994. (b) Hatfield, L. D.; Blaszczak, L. C.; Fischer, J. W. (Eli Lilly). U.S. Patent 4,226,986, 1980. (c) Hatfield, L. D.; Lunn, W. H. W.; Jackson, B. G.; Peters. L. R.; Blaszczak, L. C.; Fisher, J. W.; Gardner, J. P.; Dunigan, J. M. In *Recent Advances in the Chemistry of β-Lactam Antibiotics*; Gregory, G. I, Ed.; The Royal Society of Chemistry: London, 1980; p 109. (d) Bodurow, G. C.; Boyer, D. D.; Brennan, J.; Bunnell, C. A.; Burks, J. E.; Carr, M. A.; Doecke, C. W.; Eckrich, T. M.; Fisher, J. W.; Gardner, J. P.; Graves, B. J.; Hines, P.; Hoying, R. C.; Jackson, B. G.; Kinnick, M. D.; Kochert, C. D.; Lewis, J. S.; Luke, W. D.; Moore, L. L.; Morin, J. M., Jr.; Nist, R. L.; Prather, D. E.; Sparks, D. L.; Valduchick, W. C. *Tetrahedron Lett.* **1989**, *30*, 2321. (e) Burks, J. E., Jr.; Chelius, E. C.; Johnson, R. A., *J. Org. Chem.* **1994**, *59*, 5724.

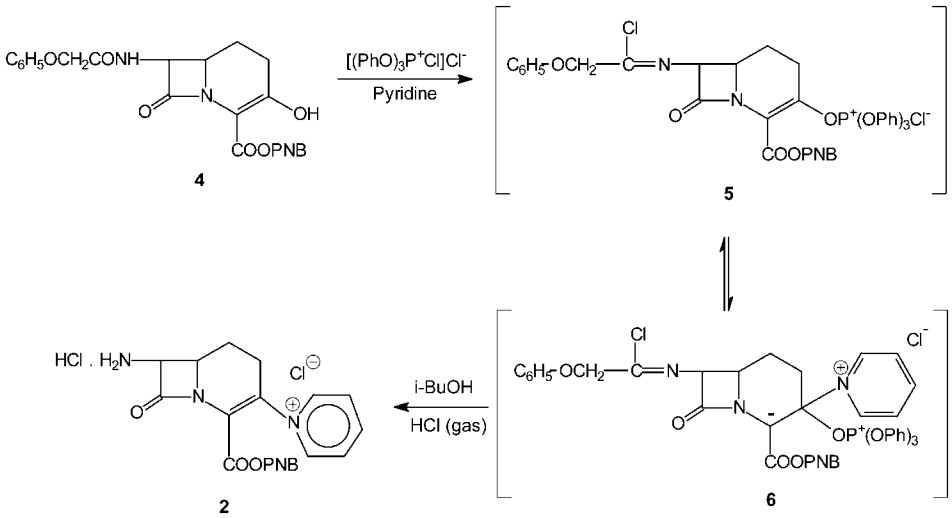
Published on Web 05/15/2003

10.1021/op034026x CCC: $25.00

Scheme 1



Scheme 2



To minimize the above impurity **2**, we turned our attention to the optimization of reaction conditions. In a typical experiment the chlorotriphenoxyphosphonium chloride [$(PhO)_3P^+ClCl^-$] prepared at low temperature (−20 to −30 °C) in dichloromethane is added to a suspension of intermediate **4** in ethyl acetate in the presence of pyridine at low temperature (−55 to −20 °C). The temperature is raised to 20−25 °C and the intermediate **1** isolated from the reaction mixture with the addition of isobutanol followed by an HCl gas sparge.

It is found that the factors which are favourable for the minimization of impurity **2** are the following: (1) addition of chlorination reagent $(PhO)_3P^+ClCl^-$ in one lot to the suspension of intermediate **4** in ethyl acetate (Table 1, entry 1); (2) addition of pyridine in two portions to the reaction mixture prohibits the formation of species **6** due to the nonavailability of excess pyridine (Table 1, entry 2). During scale-up batches where addition of chlorination reagent $(PhO)_3P^+ClCl^-$ in one lot is not feasible, this reaction condition is found to be more suitable.

Further, it is observed that slow addition of chlorination reagent $(PhO)_3P^+ClCl^-$ to the suspension of intermediate **4** in ethyl acetate (Table 1, entry 3) and addition of intermediate **4** dissolved in CH_2Cl_2 to the precooled $(PhO)_3P^+ClCl^-$ in dichloromethane in the presence of pyridine and ethyl acetate (Table 1, entry 4) favour the formation of impurity **2**. In these cases the availability of pyridine is more for attack on species **5**, resulting in the formation of species **6** (Scheme 2). Similarly when the reaction is carried out only in dichloromethane (Table 1, entry 5), due to higher solubility of intermediate **4** in dichloromethane, the reaction medium is homogeneous. These conditions are favourable for the formation of species **6**. The presence of ethyl acetate makes the reaction medium heterogeneous due to insolubility of

Table 1. **Chlorination of intermediate 4 under different conditions**

entry no	reaction conditions	impurity **2** (%) in isolated intermediate **1** (by HPLC)	yield (%) (after methanol washing)
1	typical experiment (see Experimental Section)	0.2	74[a]
2	addition of pyridine in two portions	0.2	76[a]
3	slow addition of $(PhO)_3P^+ClCl^-$ complex	15	61
4	addition of intermediate **4** to the $(PhO)_3P^+ClCl^-$ (reverse addition)	17	55
5	reaction in dichloromethane (without ethyl acetate)	13	58

[a] No methanol washing.

intermediate **4** (Table 1, entries 1 and 2). It indicates that the solubility factor also plays a role in the formation of impurity.

From the above experiments, it is evident that the ideal condition for minimization of impurity **2** is to carry out the reaction in a mixture of ethyl acetate and dichloromethane with pyridine addition in two portions, to keep excess chloride ions in the reaction medium.

Impurity **2** present in isolated intermediate **1** can be removed by washing with methanol to afford pure intermediate **1**. It can be isolated from methanol washings, and its structure has been identified by spectral data (see Experimental Section).

Conclusions

The above report describes a scalable process for the conversion of intermediate **4** to **1**. An impurity formed during the conversion is isolated and identified. The reaction conditions are optimized to minimize the impurity formation and prepare intermediate **1** in good yield and quality.

Experimental Section

General. Reagents were used as such without further purification. HPLC was performed with a Waters instrument using Kromasil C18 (150 mm × 4.6 mm, 5μm) column. ^{1}H NMR spectra were recorded using Bruker 300 MHz in DMSO-d_6. The chemical shift data is reported as δ (ppm) downfield from tetramethylsilane which was used as an internal standard. Mass spectra were recorded using API 2000 (MDS SCIEX) instrument.

Preparation of (4-Nitrophenyl)methyl, 7-Amino-1-carba(dethia)-3-chloro-3-cephem-4-carboxylate monohydrochloride (1) (Typical Experiment: Table 1, Entry 1). To a mixture of triphenyl phosphite (232 g, 0.74 mol) in dichloromethane (1000 mL) and pyridine (12 g, 0.15 mol) at ~−30 to −15 °C, chlorine gas is bubbled until light-yellow colour develops. Cyclohexene is added dropwise to decolourise the yellow colouration and stirred at ~−20 to −25°C for 10−15 min. In a separate flask, (4-nitrophenyl)-methyl, 7-phenoxyacetamido-3-hydroxy-1-carba(dethia)-3-cephem-4-carboxylate **4** (100 g, 0.214 mol) is suspended in ethyl acetate (400 mL) and pyridine (47 g, 0.59 mol). The suspension is cooled to ~−50 to −55 °C and chlorotriphenoxyphosphonium chloride solution in dichloromethane added in one lot under nitrogen atmosphere and flushed with dichloromethane (500 mL). The reaction is stirred at −20 to −25 °C for 30 min, the temperature is slowly raised to 0 °C, and the reaction is stirred for 60 min at 0−5 °C. The temperature is further raised to 20 °C and stirring continued for approximately 90 min at 20−25 °C; the reaction is monitored by HPLC for completion. Isobutanol (127 g, 1.7 mol) is added and stirred for 15−20 min at 25−30 °C followed by bubbling of HCl gas for 15−20 min at 25−30 °C. The reaction mixture is allowed to stir for 60 min at ambient temperature, cooled to 5−10 °C, and filtered. The wet cake is washed with dichloromethane (2 × 250 mL) and dried to give the desired product 61.5 g (74%).

Chromatographic purity (by HPLC): 98%, ^{1}H NMR (DMSO-d_6): 2.0 (m, 2H, CH_2), 2.4 (m, 2H, CH_2), 4.0 (m, 1H, β-lactam), 4.8 (d, J = 4.8 Hz,1H, β-lactam), 5.4 (s, 2H, $COOCH_2$−), 7.7 (d, J = 8.2 Hz, 2H, ArH), 8.2 (d, J = 8.4 Hz, 2H, ArH), 9.4 (br, 2H, NH_2).

Table 1, Entry 2. In the above experiment pyridine is added in portions. Initially 0.31 mol of pyridine is added to the suspension in ethyl acetate, and the remaining quantity, 0.28 mol, is added to the reaction mixture after stirring for 45 min at 0−5 °C. The rest of the reaction is carried out as mentioned above (yield: 76%).

Isolation of Impurity 2: (4-Nitrophenyl)methyl, 7-Amino-1-carba(dethia)-3-pyridyl-3-cephem-4-carboxylate Monohydrochloride. To a mixture of triphenyl phosphite (232 g, 0.74 mol) in dichloromethane (1000 mL) and pyridine (12 g, 0.15 mol) chlorine gas is bubbled at −30 to −15 °C until a light-yellow colour persists. Cyclohexene is added to decolourise the yellow colour, and the mixture is stirred at −30 to −35 °C for 10−15 min. Pyridine (47 g, 0.59 mol) is added followed by intermediate **4** dissolved in dichloromethane (500 mL) at −35 to −15 °C. The reaction mixture is allowed to stir for 30 min at −20 to −25 °C, 0−5 °C for 60 min and 20−25 °C for 90 min. Isobutanol (127 g, 1.7 mol) is added followed by bubbling of HCl gas at 25−30 °C. It is stirred for 60 min and then cooled to 5−10 °C, filtered, and washed with dichloromethane (2 × 250 mL) to obtain the desired product 55 g (66%). The chromatographic purity by HPLC shows 17.0% impurity **2**. The above material (55 g) is suspended in methanol (300 mL) and stirred at ambient temperature for 30 min. It is filtered, washed with methanol (100 mL), and dried to yield 45.6 g (55%) of intermediate **1**.

The methanol washings are combined and concentrated to give a residue which is triturated with ethyl acetate (100 mL) and filtered, and the hygroscopic solid is washed with ethyl acetate (50 mL) and dried under vacuum to obtain

2.5 g of impurity **2**. ^{1}H NMR (DMSO-d_6 + D_2O): 2.07 (m, 1H, CH_2), 2.1 (m, 1H, CH_2), 3.0 (m, 2H, CH_2), 4.1 (d, J = 4.8 Hz, 1H, β-lactam), 5.1 (d, J = 4.6 Hz, 1H, β-lactam), 5.2 (s, 2H, $-CH_2-$COOPNB), 7.5 (d, 2H, ArH), 8.0 (m, 2H, pyridyl H), 8.2 (m, 3H, ArH, pyridyl H), 8.9 (m, 2H, pyridyl H), 9.2 (br, 2H, NH_2), IR (KBr cm^{-1}): 3419, 2881, 1787, 1732, 1628, 1521, 1486, 1402, 1378, 1348, 1294, 1267, 751, 681, MS (*m*/*e*): 395.

Acknowledgment

We are grateful to the Analytical Division of Ranbaxy Research Laboratories for their analytical and spectral support.

Received for review February 13, 2003.

OP034026X