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Optimization of the Penicillin Ring Expansion Reaction through the Use of an Alkene as an HCl Scavenger

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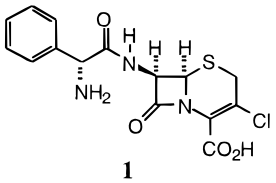
Abstract:

The combination of alkenes and $SnCl_4/Et_2O$ in the ring expansion of penicillin sulfoxides to 3-exomethylenecephams inhibits the formation of chlorine that is responsible for the production of a chlorine-substituted byproduct. These reagents block formation of chlorine from the reaction of HCl with *N*-chlorophthalimide by removal of HCl.

Introduction

Cefaclor (**1**) is an important wide spectrum antibiotic used in the treatment of a broad range of bacterial infections.[1] A key step in the production of **1** is the ring expansion of penicillin V sulfoxide *p*-nitrobenzyl ester **2** to 3-exomethylene cephalosporin V sulfoxide *p*-nitrobenzyl ester **4** (Scheme 1).[2] This conversion is capricious due to the reactivity of **2** (Scheme 2).[2] In particular, the presence of trace amounts of HCl and chlorine during the preparation of **3** may cause total loss of yield. Acid scavengers such as propylene oxide[3] or poly(vinylpyridine−divinylbenzene) (Reillex)[4] are utilized to minimize the concentration of HCl during the preparation of **3** and are required to obtain optimum yield. Although chlorine quantity was indirectly controlled through control of the concentration of HCl, the reaction protocol did not contain a direct method to control chlorine concentration.



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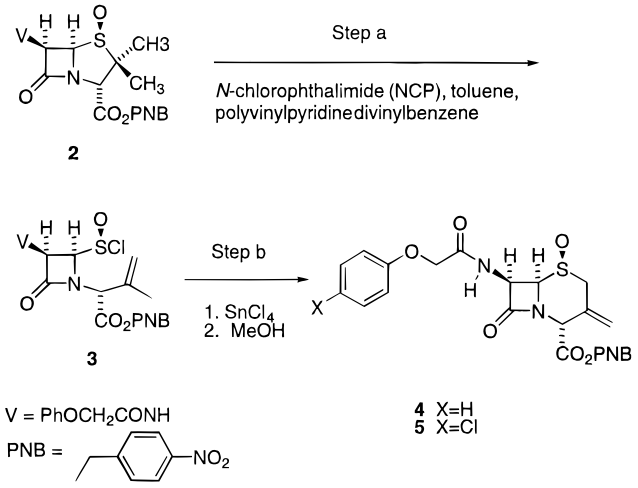
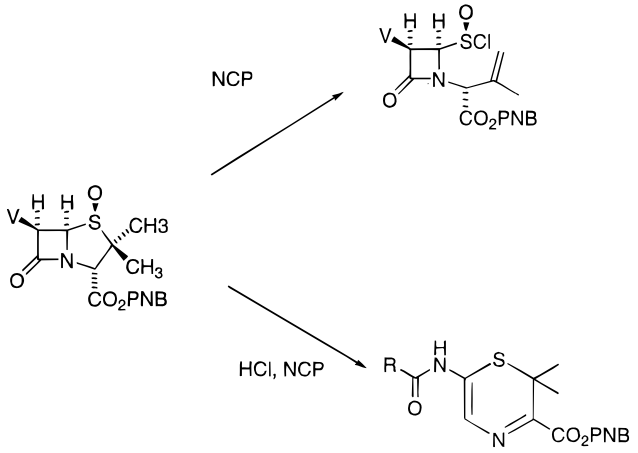
In our effort to make this process more robust, we examined the use of alkenes as possible chlorine scavengers.[5] We report herein identification of an impurity **5** resulting from the electrophilic chlorination of the phenyl ring of the V side chain and the impact of the addition of an alkene to the reaction mixture on the 3-exomethylene ring expansion reaction.

Scheme 1



Scheme 2



Results and Discussion

Initially, we examined the impact of various alkenes on the ring expansion reaction by measuring reaction yield. The results are recorded in Table 1. The data suggested that alkenes which were most beneficial were those which were unconjugated, contained no electron-donating or -withdrawing groups, and were not sterically encumbered. Additional focus was on the quality of **4** produced with and without 1-hexene. HPLC analysis indicated that an impurity was present in **4** isolated from reactions which did not employ 1-hexene. This impurity was isolated by preparative HPLC. Analytical data indicated that this impurity was **5**, which

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(3) Kukolja, S. Belgium Patent 837,040, 1976.
(4) Chou, T. S. U.S. Patent 4,289,695, 1981.
(5) Copp, J. D.; Tharp, G. A. U.S. Patent 4,950,753, 1990.

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Table 1. **The impact of yield of 4 by alkene addition to the ring expansion reaction**

alkene added	% yield improvement	alkene added	% yield improvement
1-pentene	3.0	cyclopentene	3.4
1-hexene	4.2	cyclohexene	2.9
1-tetradecene	2.0	2-hexene	3.6
2-methyl-2-butene	−3.7	methylenecyclopentane	−4.8
isoprene	−4.7	1,3-cyclohexadiene	−19.2
ethyl vinyl ether	−9.8	2,3-dihydrofuran	−14.2
methyl acrylate	−7.2	acrylonitrile	−6.9

Table 2. **Mass balance of 1-hexene added to the ring expansion step[6]**

compound	% detected
1-hexene	24.3
trans-2-hexene	6.6
cis-2-hexene	3.5
2-chlorohexane	48.4
unknown	17.2
1,2-dichlorohexane	<limit of detection

Table 3. **2-Chlorohexane formation as a function of reagents added**

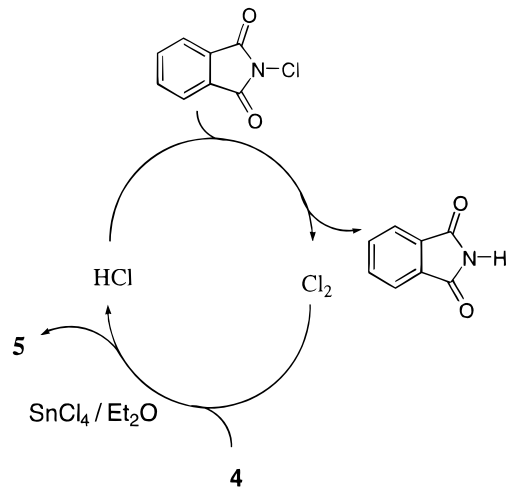
trial number	reagents added	2-chloro-hexane produced (%)	1-hexene recovered (%)
1	none (control)	<0.6	95.0
2	HCl (satd soln)	<0.6	94.5
3	$SnCl_4$(1.7 equiv)/Et_2O (0.9 equiv)	6.5	81.0
4	HCl (satd soln)/$SnCl_4$ (1.7 equiv)/ Et_2O (0.9 equiv)	82.2	10.1

resulted from chlorination at the para position of the side chain of **4**.

In an effort to determine the mechanism of action of alkenes, we studied the effect of 1-hexene using reaction yield as a tool. Initially, the yield dependence on the time of 1-hexene addition to the reaction mixture was explored through a determination of yields of reactions to which 1-hexene was added either initially or after preparation of **3**. These experiments indicated that the effect of 1-hexene occurred during the ring closure step (step b, Scheme 1) and not during the preparation of **3** (step a, Scheme 1). Additional information on the mechanism came from an examination of the toluene filtrate from the ring closure step (step b, Scheme 1). Table 2 reports the compounds observed in this analysis and a mass balance of the 1-hexene added to the reaction.[6] Identification of 2-chlorohexane indicated that 1-hexene was acting as an HCl scavenger. The presence of *cis* and *trans* isomers of 2-hexene was additional evidence for proton addition to the olefin. The absence of dichlorohexane in the reaction mixture suggested that the mode of action was not one of removal of chlorine.

Additional mechanistic understanding of the influence of 1-hexene in this reaction was gained by quantifying the 2-chlorohexane generated by treatment of a solution of 1-hexene in toluene with different reagents under the conditions of the ring expansion reaction. The data in Table 3 indicated that the addition of HCl to 1-hexene was catalyzed by the Lewis acid, $SnCl_4/Et_2O$ complex, which was utilized in affecting the ring closure of **3** to **4**.[7] The level of 6.5% of 2-chlorohexane observed in trial 3 may be due to the presence of HCl in the stannic chloride. We surmised that electrophilic attack by chlorine, catalyzed by the Lewis acid, $SnCl_4/Et_2O$ complex, was responsible for the chlorination of the phenyl ring. Such a process could be catalytic in HCl (Scheme 3).

Scheme 3



The source of the chlorine was the reaction of HCl with the residual NCP. This was demonstrated by the results of a series of experiments which determined what reaction conditions were responsible for production of **5** (Table 4).[8] As the data in Table 4 demonstrate, maximum chlorination of **4** required NCP, HCl, and $SnCl_4/Et_2O$ complex, which supported the conclusion that the Lewis acid is required. Support for the generation of **5** from chlorine and the $SnCl_4/Et_2O$ complex comes from line 4.[9]

In summary, the addition of 1-hexene or other unsubstituted *n*-terminal or internal olefins to the ring closure step

(6) Analysis was accomplished by vapor phase chromatography using a 30 m DB1701 capillary column and a He flow of 1.0 mL/min where the temperature was held for 8.0 min. A split ratio of 20:1 was used.

(7) Other investigators have reported Lewis acid catalyzed additions of HCl to olefins. (a) Mechoulam, R.; Braun, P.; Gaoni, Y. *J. Am. Chem. Soc.* **1972**, *94*, 6159. (b) Makriyannis, A.; Banijamali, A. R. *J. Heterocycl. Chem.* **1988**, *25*, 823.

(8) The amount of **5** in each experiment was determined by HPLC analysis. HPLC conditions: column, 25 cm Zorbax C-8 (5 μm packing); flow rate, 1.5 mL/min; detection wavelength, 254 nm. Eluent: solvent A = 0.05 M NH_4OAc, and solvent B = 9:1 ACN/H_2O (ACN = acetonitrile); the gradient profile was held for 1.0 min at 100% A and then ramped up to 100% B over 32 min (approximately 3%/min), where it was held for 2.0 min.

(9) The low level of **5** observed may have been due to the relative insolubility of the reagents under the conditions of the reaction in this experiment. In particular, the exomethylene/stannic chloride complex was very insoluble.

Table 4. **The influence of reaction conditions on formation of 5 from 4**

reaction no.	reaction conditions	% **5**
1	NCP, anhydrous HCl	0
2	NCP, $SnCl_4/Et_2O$	0
3	NCP, HCl, $SnCl_4/Et_2O$	20.6
4	Cl_2, $SnCl_4/Et_2O$	1.0

of **3** resulted in reduction of **5**. The mechanism by which the 1-hexene was operating was demonstrated to be one in which the 1-hexene in conjunction with the Lewis acid, $SnCl_4/Et_2O$ complex, served as a scavenger of hydrogen chloride.[10] This reduces the quantity of chlorine resulting from the reaction of HCl with NCP in the reaction mixture. The reduction of **5** was due to the minimization of chlorine which was necessary for the electrophilic chlorination of the aromatic side chain of **4**.

Experimental Section

The weights of *p*-nitrobenzyl ester of penicillin V sulfoxide **2** and exomethylene cephalosporin V sulfoxide *p*-nitrobenzyl ester **4** have been potency corrected using HPLC. HPLC conditions for the quantitation of **5** are listed in footnote 8. NMR spectra were obtained using a General Electric QE-300 (300 MHz) spectrometer. High-resolution mass spectra were obtained on a VG-ZAB2SE spectrometer using a magic bullet matrix.

Preparation of Exomethylene Cephalosporin V Sulfoxide *p*-Nitrobenzyl Ester 4 with Added 1-Hexene. A slurry of 16.2 g of poly(vinylpyridine−divinylbenzene) in 800 mL of toluene was heated to reflux, and 200 mL of a water/toluene mixture was removed by azeotropic distillation. The slurry was cooled to 60 °C, and 48.2 g (0.096 mol, 1.0 equiv) of *p*-nitrobenzyl ester penicillin V sulfoxide **2** and 21.6 g (0.119 mol, 1.2 equiv) of *N*-chlorophthalimide were added. This mixture was heated at reflux for 100 min. During the reflux, an additional 40 mL of toluene was removed *via* distillation. The resultant solution of sulfinyl chloride **3** was cooled to 10 °C, the phthalimide and poly(vinylpyridine−divinylbenzene) were removed *via* vacuum filtration, and the filter cake was washed with 100 mL of toluene. The filtrate was cooled to 10 °C, and 12 mL (0.096 mol, 1.0 equiv) of 1-hexene was added. In a separate flask, a solution of 9.2 mL (0.089 mol, 0.9 equiv) of anhydrous Et_2O in 25 mL of toluene was prepared. This mixture was cooled to 0−5 °C, and 19 mL (0.164 mol, 1.71 equiv) of $SnCl_4$ was added, while a temperature between 0 and 5 °C was maintained. The solution of **3** was cooled to 10 °C, and the $SnCl_4/Et_2O$ mixture was added. The resultant reaction mixture was allowed to warm to 25−30 °C and was stirred at this temperature for 6 h. The resultant tin complex of **4** was isolated *via* vacuum filtration and washed with 80 mL of toluene. The filter cake was then reslurried in 250 mL of MeOH, was stirred at 25−30 °C for 15 min, and was then stirred for an additional 3.75 h at 0−5 °C. The solids were isolated *via* vacuum filtration, and the cake was washed with 100 mL of MeOH and dried *in vacuo* at 48 °C overnight, to afford 35.5 g (74.0%) of **4**.

Preparation of *p*-Chloro Exomethylene Cephalosporin V Sulfoxide *p*-Nitrobenzyl Ester 5. A toluene solution of sulfinyl chloride **3** (prepared in the same fashion as described above for use in the preparation of **4**) was concentrated *in vacuo* to a thick oil. The oil was dissolved in 600 mL of CH_2Cl_2, and 43.2 g (0.192 mol, 2.0 equiv) of *N*-chlorophthalimide was added. This mixture was stirred at 10−20 °C until all the *N*-chlorophthalimide was dissolved and then cooled to 0 °C. A mixture of 19 mL (0.164 mol, 1.71 equiv) of $SnCl_4$ and 9.2 mL (0.089 mol, 0.93 equiv) of anhydrous Et_2O in 25 mL of toluene was added to the previous chilled solution. The resultant heterogeneous mixture was stirred overnight at room temperature. The resultant solids were isolated *via* vacuum filtration and washed with 80 mL of toluene. The filter cake was reslurried in 250 mL of MeOH, and the mixture was stirred at 25−30 °C for 15 min and then for 3.75 h at 0−5 °C. The solids were isolated *via* vacuum filtration and washed with 100 mL of MeOH. The resultant mixture of *p*-chloro **5** and phthalimide was slurried in 500 mL of CH_2Cl_2 at room temperature for 15 min and the insoluble phthalimide removed *via* vacuum filtration. The filtrate was extracted three times with 300 mL of 10% aqueous potassium carbonate and two times with 500 mL of saturated aqueous sodium chloride. The organic layer was dried over magnesium sulfate and concentrated, *in vacuo*, to afford an off-white solid. This solid was recrystallized from acetonitrile, to afford 13.0 g (27.0%, potency corrected by HPLC) of *p*-chloro exomethylene **5** as white needles: mp 168−170 °C; ^{1}H NMR ($CDCl_3$ and DMSO-d_6) δ 3.58 (d, 1H, J = 14 Hz), 3.77 (d, 1H, J = 14 Hz), 4.52 (s, 2H), 4.92 (d, 1H, J = 5 Hz), 5.28 (s, 2H), 5.31 (s, 1H), 5.50 (s, 1H), 5.79 (s, 1H), 6.02 (dd, 1H, J = 5, 10 Hz), 6.83 (d, 2H, J = 7.5 Hz), 7.22 (d, 2H, J = 7.5 Hz), 7.50 (d, 2H, J = 7.5 Hz), 8.10 (d, 1H, J = 10 Hz), 8.25 (d, 2H, J = 7.5 Hz); IR (KBr) 3410, 1771, 1748, 1709, 832 cm^{-1}; HRMS (MH^+) found 534.0742, calcd for $C_{23}H_{20}N_3O_8SCl$ (MH^+) 534.0738.

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(10) The yield of reactions utilizing other acid scavengers such as epoxides was lower than the control yield. Due to the hetereogeneous nature of the reaction at this point, the use of Reillix as an acid scavanger was not possible for this application.