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AN EFFECTIVE AND CONVENIENT ESTERIFICATION OF CEPHALOSPORIN DERIVATIVES BY USING QUARTERNARY AMMONIUM SALTS AS CATALYSTS

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Abstract : A method for preparing cephalosporin derivatives by reacting cephalosporin alkaline metal salts with organic halide in the presence of quarternary ammonium salts catalyst is disclosed. Δ^3 to Δ^2 isomerization, a side reaction commonly reported in preparation of cephalosporin derivatives, was successfully eliminated. The desired Δ^3 was obtained as a sole product in the reaction.

Recently, remarkable developments have been achieved with respect to β-lactam antibiotics. The cephalosporins bearing an aminothiazole-oxime moiety at the C-7 position of the cephem nucleus, so-called third generation cephalosporins[1-4], have been developed clinically as parenteral antibiotics. They possess a wide antimicrobial spectra against Gram-positive and Gram-negative bacteria and an increased resistance against bacterial β-lactamases. Although many cephalosporin derivatives which exhibit excellent antibacterial activity have been discovered, most of them are for parenteral administration. However, except

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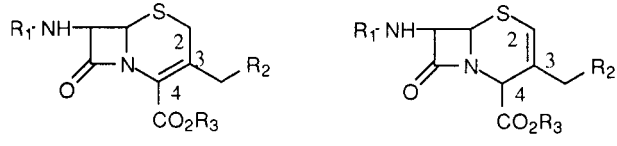
where massive dose of an antibiotics is to be administered quickly, the preferred route of administration is oral, as oral preparations can be administered by the patient himself without the need for trained supervision or assistance.

Unfortunately, of the many cephalosporin derivatives discovered, very few possess a combination of superior antibacterial activity, broad antibacterial spectrum and the ability to be absorbed efficiently through the digestive tract. This is thought to be due to the strong dissociation of the carboxylic group at the C-4 of cephem nucleus (i. e. the low *pka* value) and the strong acidity. For this reason many efforts have been made to improve the absorption of cephalosporin derivatives through the digestive tract by esterifying the C-4 carboxylic group. The prodrug approach has been frequently utilized in penicillins to give a lipophilicity which is known to be one of the important factor in the passive absorption from the intestinal tract[5-7].

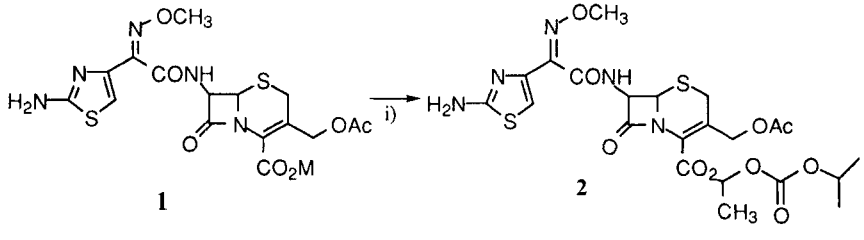
A serious problem often encountered in C-4 esterification on cephem nucleus is the tendency of the Δ^3 double bond to migrate into the more stable Δ^2 position, even under slightly basic conditions. Moreover, in the preparation of cephalosporin ester prodrugs, Δ^3 to Δ^2 isomerization was frequently reported to occur in various reaction conditions[8]. The difference between Δ^3 and Δ^2 isomeric compounds are shown as Scheme 1.



Δ^3 Ceph-3-em Δ^2 Ceph-2-em

Scheme 1.

Δ^2 isomers are unreactive as antibacterial agents. Because of the structure similarity, these undesired by-products are very difficult to separate from the desired Δ^3 isomers. A method of transforming Δ^2 isomers to Δ^3 isomers is commonly adopted[9]. This method involves two steps of reactions where the Δ^2 isomers are oxidized to their sulfoxide derivatives. The sulfoxides are then transformed back to the desired Δ^3 isomers upon sodium thionate reduction. However, the two-steps reactions along with relevant isolation and purification processes make this method uneconomical. Recently, T.P. Demuth[10] et al and S. Mobashery et al[11] reported methods to prepare cephem ester by using cephem acid as the starting materials instead of metal salts . However, the cephem metal salts have to be transformed to their free acid prior to the reaction and the method in preventing Δ^3 to Δ^2 isomerization is only applicable to certain cephem compounds with a limited solvent system as reaction media. The limitation makes the process not universal and not practical for preparation of cephem esters. As a result of our extensive studies, now we wish to report a new and advanced method for esterification on the C-4 carboxylic acid of the cephalosporin derivatives using quarternary ammonium salts as phase transfer catalysts($nBu_4N^+X^-$).



Reagents and condition : i) $nBu_4N^+HSO_4^-$, $Cl\text{-}CH_2O\text{-}CO_2CH(CH_3)_2$, DMF, 40~45 °C, 18 h

Scheme 2.

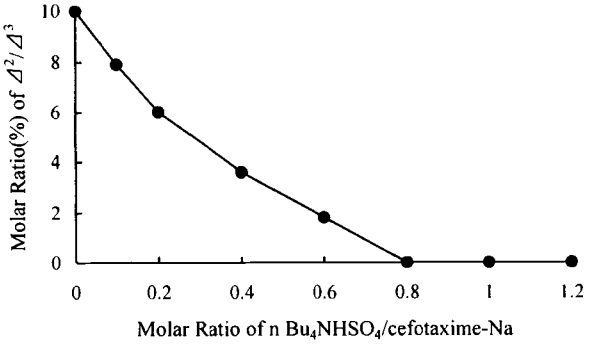
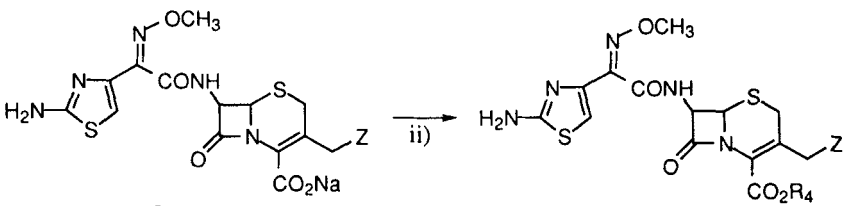


Fig. 1. The molar ratio of Δ^2 / Δ^3 of cefotaxime-sodium by using $nBu_4N^+HSO_4^-$ molar ratio

In general, the quarternary ammonium salts ($nBu_4N^+X^-$)[12] are stable compounds during storage at room temperature, soluble in most of organic solvents, readily accessible, commercially available and inexpensive even in large scale. In order to demonstrate the simplicity and versatility, cefotaxime sodium **1** was directly treated with tetra-n-butyl ammonium hydrogensulfate and 1-chloro ethyl isopropyl carbonate. The esterification of carboxylic acid of cefotaxime sodium with unprotected amino group was carried out successfully by the treatment of one equivalent alkyl halide and 10mol% phase transfer catalyst ($nBu_4N^+HSO_4^-$) in the presence of DMF. Monitoring of the reaction by HPLC and TLC showed that the formation of the esterification product **2** was usually completed with in 18~24 h at 40~45 °C. The significance of using quarternary ammonium salt with acidic counter ion as catalyst reaction medium is demonstrated in Fig. 1.

Referring to Fig. 1, the drawing shows the effect of $TBA^+HSO_4^-$ on prevention of esterification of cefotaxime sodium from undesired Δ^3 to Δ^2 isomerization (Scheme 1).

The abscissa represents the molar ratio of TBA $^+HSO_4^-$ /cefotaxime sodium used in the reaction and the axis of ordinate denotes the molar ratio of undesired Δ^2 to desired Δ^3 product, obtained from the reaction and monitored by HPLC. As shown in the figure, a significant amount of Δ^2 isomer was obtained in the reactions where phase transfer catalyst was not added (10 molar ratio of Δ^3 vs Δ^2). Isomerization was completly inhibited when the ratio reached 8mol% of TBA $^+$ HSO_4^-, the desired Δ^3 isomer was obtained as the sole product.



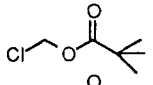
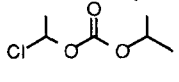
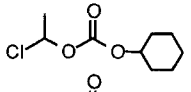
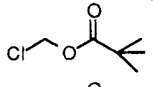
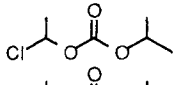
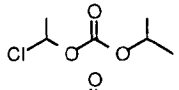
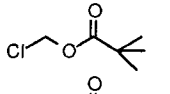
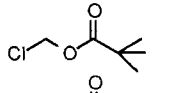
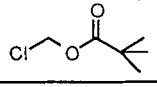
3 4

Reagents and condition : ii) $nBu_4N^+X^-$, R_4-Cl.

Scheme 3.

The esterification reactions were accomplished within 18~24 h by adding phase transfer catalysts at 40~45 °C. The desired products **4** were obtained according to the general procedure in the experimental section. These reaction conditions have been applied to the preparation of several alkyl halides and various quarternary ammonium salts, as phase transfer catalysts. The results are summarized in Scheme 3 and Table 1.The reaction clearly demonstrated that the esterification reaction could be facilitated by the addition of quarternary ammonium salt as catalyst and the Δ^3 to Δ^2 isomerization, commonly reported, could be fully eliminated when quarternary ammonium salts with bromide, iodide, hydrogen sulfate, and p-toluene sulfate were used catalyst.

Table 1. The preparation of cephalosporin prodrug derivatives 4 by several conditions.

Entry	R 4-Cl	Z	$nBu_4N^+X^-$	Solvent	Rxn Time (h) [a]	Yield(%) [b]
1		OAc	nBu_4NHSO_4	DMF	18	88
2		OAc	nBu_4NHSO_4	DMF	20	82
3		OAc	nBu_4NHSO_4	DMF	24	78
4		OAc	nBu_4NI	DMF	22	62
5		OAc	nBu_4NBr	DMF	20	68
6		$CH=CH_2$	nBu_4NHSO_4	DMF	18	81
7		$CH=CH_2$	nBu_4NTsOH	DMF	20	76
8		$CH=CH_2$	nBu_4NHSO_4	DMF-H_2O	30	54
9		$CH=CH_2$	nBu_4NHSO_4	THF-H_2O	38	38

a) Esterification reaction carried out at a ranging from -10 °C to 0 °C temperature.

b) Isolated yield based on cephalosporin derivatives **3** used.

Experimental Section

All reactions were conducted anhydrous conditions in solvents dried over molecular sieves 4A under nitrogen atmosphere. IR spectra were taken on a Nicolet FT-IR 205 spectrometer. ^1H NMR spectra were recorded on a Bruker DPX 400MHz spectrometer using TMS or sodium 2,2-dimethyl-2-silapentane-5-sulfonate(in D_2O) as an internal standard. The coupling constants (J) are reported

in Hz. Merck silica gel 60 (70~230mesh) was used for column chromatography. The yields reported are for the chromatographically pure isolated products. Tetrabutyl ammonium iodide and tetrabutyl ammonium hydrogen sulfate were purchased from Signa & Aldrich. Tetra butyl ammonium p-toluene sulfonate and tetrabutyl ammonium bromide were purchased from Acros and Aldrich, respectively.

1-(Isopropoxycarbonyloxy)ethyl 7β-[2-(2-aminothiazol-4-yl)-(Z)-methoxyiminoacetamido]-3-acetoxymethyl-3-cephem-4-carboxylate(2). General procedure for the preparation of compound (4).

To a stirred solution of cefotaxime sodium 3 (1.4 g, 0.30 mmol) in DMF (15 mL) at room temperature, after 30min stirred, was added 1-chloroethyl isopropyl carbonate (0.5 g, 3.0 mmol). After reaction mixture was stirred at 40~45 °C for 18 h, the reaction mixture was diluted with EtOAc (100 mL) and washed successively with water (20 mL) and brine (80 mL). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo* to give a slightly yellow-white solid. The solid was chromatographed on a silica gel column (EtOAc : n-Hexane = 3 : 1) to give **2** : yield 1.40 g, 82% ; mp 124 - 129 °C (decomp) ; IR (KBr, cm^{-1}) 1780 (β-lactam C=O), 1680 (amide C=O); ^1H NMR (400 MHz, $CDCl_3$) δ 1.31(6 H, d, *J*=6.0 Hz, $CH(CH_3)_2$), 1.56(3 H, d, *J*=5.5 Hz, $CHCH_3$) 1.82(3 H, s, $COCH_3$), 3.52(2 H, s, 2-CH_2), 4.01(3 H, s, $NOCH_3$), 4.31(2 H, s, 3'-CH_2), 4.5~5.2(1 H, m, $CH(CH_3)_2$), 5.06(1 H, d, *J*=5.0 Hz, 6-CH), 6.05(1 H, dd, *J* =5 & 9 Hz, 7-CH), 6.72(1 H, thiazol-H), 7.88 & 7.96(1 H, q x 2, *J*=5.5 Hz, $CHCH_3$), 8.06 and 8.10(1 H, d x 2, *J*=9.0, 7-NHCO). Anal. ($C_{22}H_{27}N_5O_{10}S_2$) C, H, and N.

Pivaloyloxymethyl 7β-[2-(2-aminothiazol-4-yl)-(Z)-2-methoyiminoacetamido]-3-acetoxymethyl-3-cephem-4-carboxylate (1).

The preparation of compound 1 was carried out by a similar method mentioned

above : yield 1.50 g, 88% ; mp 107 - 115 °C (decomp); IR(KBr, cm^{-1}) 1785, 1680 ; ^1H NMR (400 MHz, $CDCl_3$) δ 1.23(9 H, s, t-butyl), 1.81(3 H, s, $COCH_3$), 3.56(2 H, s, 2-CH_2), 4.03(3 H, s, $NOCH_3$), 4.31(2 H, s, 3'-CH_2), 5.08(1 H, d, *J*=5.0 Hz, 6-CH), 5.79(2 H, brs, NH_2), 5.88(2 H, s, CH_2), 6.02(1 H, dd, *J*=5.0 & 9.0 Hz, 7-CH), 6.70(1 H, s, thiazol-H), 8.11(1 H, d, *J*=9.0 Hz, 7-NHCO). Anal. ($C_{22}H_{27}N_5O_9S_2$) C, H, and N.

1-(Cyclohexyloxycarbonyloxy)ethyl 7β-[2-(2-aminothiazol-4-yl)-(Z)-2-methoxyiminoacetamido]-3-acetoxymethyl-3-cephem-4-carboxylate (3).

The preparation of compound 3 was carried out by a similar method mentioned above: yield 1.42 g, 78% ; mp 127 - 131 °C (decomp); IR (KBr, cm^{-1}) 1780, 1750, 1680, 1540 ; ^1H NMR (400 MHz, $CDCl_3$) δ 1.0~2.2(10 H, m), 1.58(3 H, d, *J*=5.5 Hz, $CHCH_3$), 1.81(3 H, s, $COCH_3$), 3.58(2 H, s, 2-CH_2), 4.00(3 H, s, $NOCH_3$), 4.35(2 H, s, 3'-CH_2), 4.55~5.00(1 H, m, $CH(CH_3)_2$), 5.08(1 H, d, *J*=5.0 Hz, 6-CH), 6.05(1 H, dd, *J*=5.0 & 9.0 Hz, 7-CH), 6.78(1 H, s, thiazol-H), 7.77~7.96(1 H, q x 2, *J*=5.5 Hz, $CHCH_3$), 8.05 & 8.25(1 H, d x 2, *J*=9.0 Hz, 7-NHCO). Anal. ($C_{25}H_{31}N_5O_{10}S_2$) C, H, and N.

1-(Isopropoxycarbonyloxy)ethyl 7β-[2-(2-aminothiazol-4-yl)-(Z)-2-methoxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylate (6).

The preparation of compound 6 was carried out by a similar method mentioned above. Purification by silica gel chromatography (EtOAc : n-hexane = 4 : 1) : yield 1.41 g, 81% ; mp 140 - 143 °C (decomp); IR (KBr, cm^{-1}) 1780, 1750, 1685 ; ^1H NMR (400 MHz, $CDCl_3$) δ 1.31 (6 H, d, *J*=8.0 Hz, $CH(CH_3)_2$), 1.56(3 H, d, *J*= 5.5 Hz, $CHCH_3$), 3.59(1 H, d, *J*=4.5 Hz, 2-CH), 3.84(1 H, d, *J*=4.8 Hz, 2-CH), 4.01(3 H, s, $NOCH_3$), 4.50~4.92(1 H, m, $CH(CH_3)_2$), 5.06(1 H, d, *J*=5.0 Hz, 6-CH), 5.32(1 H, d, *J*=12.0 Hz, $CH=CH_2$), 5.60(1 H, d, *J*=17.5 Hz, $CH=CH_2$), 6.05(1

H, dd, *J*=5 & 7.0 Hz, 7-CH), 6.72(1 H, s, thiazol-H), 6.89(1 H, m, $CH=CH_2$), 7.85 & 7.96(1 H, q x 2, *J*=5.5 Hz, $CHCH_3$), 8.05 & 8.10(1 H, d x 2, *J*=9.0 Hz, 7-NHCO). Anal. ($C_{21}H_{25}N_5O_8S_2$) C, H, and N.

Pivaloyloxymethyl 7β-[2-(2-aminothiazol-4yl)-(Z)-2-methoxyiminoacetamido]-3-vinyl-4-carboxylate (7).

The esterification of compound 7 was carried out by a similar method mentioned above : yield 1.1 g, 76% ; mp 119 -124 °C (decomp); IR (KBr, cm^{-1}) 1780, 1680 ; ^1H NMR (400 MHz, $CDCl_3$) δ 1.23(9 H, s, t-butyl), 3.56(2 H, s, CH_2), 4.01(3 H, s, $NOCH_3$), 5.06(1 H, d, *J*=5.0 Hz, 6-CH), 5.31(1 H, d, *J*=11.5 Hz, $CH=CH_2$), 5.60(1 H, d, *J*=17.5 Hz, $CH=CH_2$), 6.05(1 H, dd, *J*=5.5 Hz & 7.5 Hz, 7-CH), 6.85(1 H, s, thiazol-H), 6.89(1H, m, $CH=CH_2$). Anal. ($C_{21}H_{25}N_5O_7S_2$) C, H, and N.

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