[Chem. Pharm. Bull. 36(7)2346—2353(1988)]

A New Synthesis of 3-Chloro-2-(thiazol-4-yl)propenoic Acid and Its Application to Cephalosporins

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(Received December 22, 1987)

Three step transformations of α-formylation, chlorination and hydrolysis starting from ethyl 4-thiazoleacetate (**1**) afforded a new cephem 7-side chain acid, (*E*)-3-chloro-2-(thiazol-4-yl)propenoic acid (**4**-(*E*)). The presence of the corresponding **4**-(*Z*) derived from photoisomerization of **4**-(*E*) was confirmed by nuclear magnetic resonance analysis. Acylation of several 7-aminocephalosporins was conducted by two routes involving the photoisomerization of **4**-(*E*) to **4**-(*Z*) (method A) or the isomerization of the activated intermediate (formula III) of the carboxylic acid **4**-(*E*) with Vilsmeier reagent by heating (method B). The synthesis and the antibacterial activities of a new series of geometrical isomers of 7-[3-chloro-2-(thiazol-4-yl)propenamido] cephalosporins (formula II) are described.

Keywords——3-chloro-2-(thiazol-4-yl)propenoic acid; ^{13}C-NMR data; α-formylation; isomerization; Vilsmeier reagent; cephalosporin

The (*Z*)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido group has been widely utilized as the side chain at the 7-position of recently developed β-lactam antibiotics.[1] Aside from this oxyimino functional group, we have studied several kinds of novel cephalosporins (formula I).[2] Each of them has a functionalized carbon–carbon double bond moiety instead of the carbon–nitrogen double bond at the α-position to the 2-(2-aminothiazol-4-yl)acetamido group.

Among many synthesized derivatives, we selected 7-[(*Z*)-2-(2-aminothiazol-4-yl)-3-chloropropenamido]-3-[4-(2-carbamoylethyl)pyridiniummethyl]-3-cephem-4-carboxylate (SG-164) as the best compound for more extensive evaluation.[3] It showed a wide spectrum of antibacterial activity not only against gram-negative bacteria but also against gram-positive ones, including β-lactamase-producing strains, and high stability to β-lactamases.

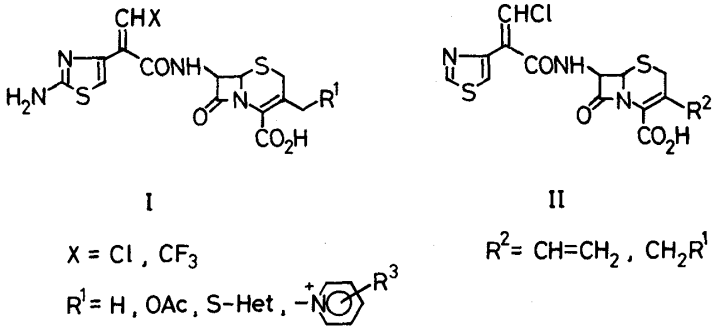


Fig. 1

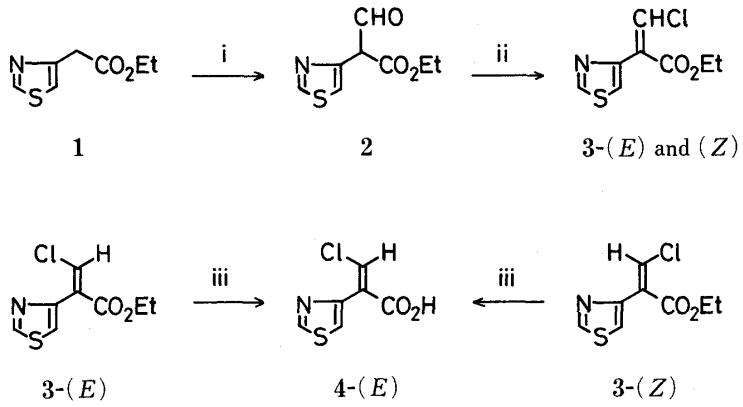
As the heteroaromatic moiety of the side chain at the 7-position of a cephem nucleus, thiazole itself without the annular amino group is also considered to be an effective functional group.[4] This paper describes a new synthesis of geometrical isomers (**4**-(*Z*) and **4**-(*E*)) of 3-chloro-2-(thiazol-4-yl)propenoic acids and their application to cephalosporins (formula II), as well as the antibacterial activities of the products.

α-Formylation of ethyl 4-thiazoleacetate (**1**)[5] with sodium hydride and ethyl formate in *N*,*N*-dimethylformamide (DMF) gave **2**[6] in 98% yield. Treatment of **2** at 0 °C with Vilsmeier reagent[7] prepared from DMF and phosphorus oxychloride afforded 3-(*E*) in quantitative yield. Chlorination of **2** with the same reagent at 100 °C gave **3**-(*E*) and **3**-(*Z*) in 72% and 11% yields, respectively. Their configurations were assigned on the basis of proton nuclear magnetic resonance (^{1}H-NMR) spectra and ^{13}C-H coupling constants (*vide infra*).

Here we tried direct deamination of ethyl (*Z*)-3-chloro-2-(2-aminothiazol-4-yl)propenoate[2a] with *tert*-butyl nitrite,[4a] but no **3**-(*Z*) was obtained.

Hydrolysis of **3**-(*E*) with potassium hydroxide in aqueous tetrahydrofuran (THF) and subsequent acidification with hydrochloric acid at 0 °C gave **4**-(*E*) in 96% yield.

Treatment of **3**-(*Z*) under the same hydrolysis conditions and subsequent work-up unexpectedly gave **4**-(*E*), suggesting that (*Z*)-3-chloro-2-(thiazol-4-yl)propenoic acid [**4**-(*Z*)] was readily isomerized to **4**-(*E*) under acidic reaction conditions.



1 2 3-(*E*) and (*Z*)

3-(*E*) 4-(*E*) 3-(*Z*)

i) NaH, HCO_2Et ii) $POCl_3$–DMF iii) a) KOH, H_2O–THF b) aq. HCl

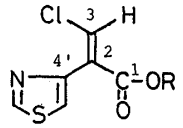
Chart 1

As it appeared that **4**-(*Z*) was thermodynamically less stable than **4**-(*E*), we tried to isomerize **4**-(*E*) directly to **4**-(*Z*) under neutral conditions. Irradiation of **4**-(*E*) in acetone-d_6 with a high-pressure mercury lamp gave a mixture of **4**-(*Z*) and **4**-(*E*) in the ratio of *ca.* 1 : 2. Although pure **4**-(*E*) was a colorless stable crystalline solid, we could not isolate **4**-(*Z*) in a pure form. The concentrated mixture of **4**-(*E*) and **4**-(*Z*) was found to be relatively unstable and hygroscopic when allowed to stand in contact with the atmosphere. The slow decomposition of the mixture seems to be connected with the acidity of the resulting mixture, because the hydrogen chloride evolved accelerates the isomerization of **4**-(*Z*) to **4**-(*E*) and the further decomposition of the mixture.

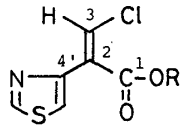
The carbon-13 nuclear magnetic resonance (^{13}C-NMR) data for **4**-(*Z*) were obtained from the above photo-irradiated reaction mixture in comparison with the data for **4**-(*E*). Selected ^{1}H- and ^{13}C-NMR data for the isomeric esters **3** and their corresponding carboxylic acids **4** are listed in Table I.

The isomer which showed the greater vicinal ^{13}C-H coupling constant J_{C1-H3} and the smaller $J_{C4'-H3}$ was assigned as the (*Z*)-isomer.[8] The other isomer was assigned as the (*E*)-isomer. The coupling constants of J_{C1-H3} and $J_{C4'-H3}$ for the same geometrical isomers of the

TABLE I. Selected ^{1}H- and ^{13}C-NMR Chemical Shifts and Coupling Constants of the Esters **3** and the Corresponding Carboxylic Acids **4**



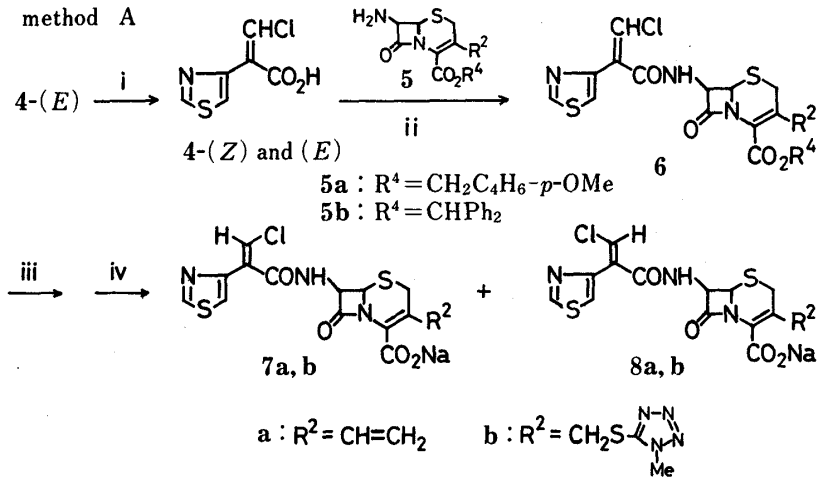
3-(*E*): R=Et
4-(*E*): R=H



3-(*Z*): R=Et
4-(*Z*): R=H

Compound	Chemical shift (ppm)					Coupling constant (Hz)	
	H3	C1	C2	C3	C4′	C1–H3	C4′–H3
3-(*E*)[a]	7.62	164.2	130.2	133.9	147.1	4	8
3-(*Z*)[a]	7.47	165.1	130.9	125.1	149.4	10	5
4-(*E*)[b]	7.78	165.8	131.0	135.2	148.5	5	9
4-(*Z*)[b]	7.46	166.8	133.7	118.0	150.6	10	5

a) In $CDCl_3$. *b*) In acetone-d_6.



i) *hv*, acetone ii) DCC iii) CF_3CO_2H iv) aq. $NaHCO_3$

Chart 2

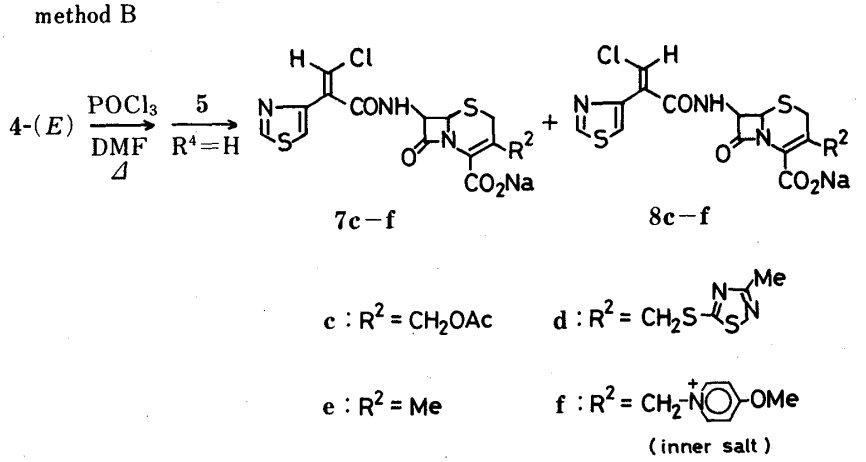
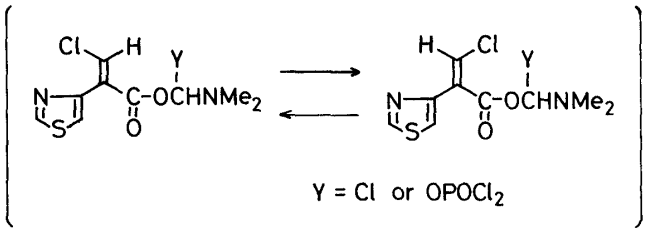


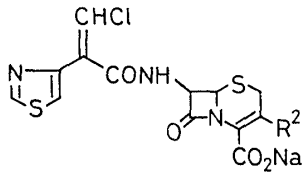
Chart 3



III

Chart 4

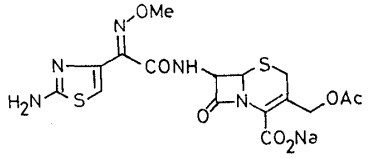
TABLE II. Antibacterial Activities (MIC, μg/ml) of Chloromethylenethiazole Cephem Derivatives



No.	7c	8c	7b	8b	7d	8d	7f	8f	7e	7a	
Compound R^2	CH_2OAc		CH_2S-(N-N, N, N, Me)		CH_2S-(Me, N, N, S)		CH_2-N$^+$(OMe)- (inner salt)		Me	$CH=CH_2$	CTX[a]
Config.	*Z*	*E*	*Z*	*E*	*Z*	*E*	*Z*	*E*	*Z*	*Z*	
S. aureus 209-P	1.56	12.5	0.39	3.13	0.39	0.39	0.1	0.39	25	25	3.13
E. coli NIHJ JC-2	0.2	1.56	0.1	1.56	1.56	12.5	0.1	6.25	25	100	0.01
K. pneumoniae 8045	0.78	50	0.2	6.25	1.56	25	0.2	25	100	>100	0.02
P. vulgaris 6897	0.1	12.5	0.02	0.01	0.05	0.78	0.2	12.5	12.5	100	0.01
E. cloacae F1510	0.78	25	0.01	0.05	1.56	0.39	0.39	12.5	>100	>100	0.78

MIC: minimum inhibitory concentration.

a)



CTX

esters and the carboxylic acids were almost the same. The H3 proton of each (*E*)-isomer was more deshielded by the carbonyl group than that of the corresponding (*Z*)-isomer.

We used two different methods to prepare the cephalosporin derivatives (see Charts 2 and 3). According to method A, the solution of the **4**-(*E*) and **4**-(*Z*) mixture obtained after photoirradiation was concentrated and the resulting residue was used immediately for further acylation of the 7-aminocephalosporins **5a** and **5b** using *N*,*N*′-dicyclohexylcarbodiimide (DCC) as the condensing agent.

Method B was the activation of **4**-(*E*) with Vilsmeier reagent followed by isomerization of the activated intermediate by heating.[2a] Thus **4**-(*E*) was treated with Vilsmeier reagent and isomerized by heating at 40 °C for 1.5 h. The resulting mixture was treated with 7-aminocephalosporanic acid derivatives **5c**—**f** to give the geometrical isomers of **7c**—**f** and **8c**—**f** (*ca.* 1 : 3), which were separated by reversed-phase silica gel column chromatography. The latter isomerization might have proceeded through the activated intermediate III

produced from **4**-(*E*) and the iminium salt prepared from phosphorus oxychloride and DMF.

Antibacterial activities of the synthesized cephalosporins against the microorganisms tested are summarized in Table II along with those of cefotaxime (CTX).

The (*Z*)-isomers (**7b**, **7c**, **7d** and **7f**) were more active than the corresponding (*E*)-isomers (**8b**, **8c**, **8d** and **8f**) against the microorganisms tested. Similar structure–activity relationships were reported for the substituted methylene[2,3] and oxyimino[9] cephem derivatives. The compounds (**7b**—**7d**, **7f** and **8f**) showed strong inhibitory activities against gram-positive bacteria, which were generally superior to that of reference CTX and were nearly equal to or slightly less than that of CTX against gram-negative bacteria. Of these compounds, the cephalosporins (**7b** and **7f**) having a thiomethyl or pyridiniummethyl group at the 3-position showed the most potent antibacterial activities against gram-positive and gram-negative bacteria. Substitution at the 3-position by a methyl or vinyl group caused a marked decrease in activity. A methyl group substituted with a leaving group such as acyloxy, heteroarylthio or pyridinium group, was necessary to maintain strong antibacterial activity.

Experimental

Melting points were taken on a Yanagimoto melting point apparatus, and are uncorrected. ^{1}H-NMR were obtained on a Varian EM-390 or Hitachi R-90H spectrometer at 90 MHz or a Bruker AM-400 spectrometer at 400 MHz; chemical shifts are given in ppm units from the tetramethylsilane standard. ^{13}C-NMR spectra were recorded using tetramethylsilane as an internal standard on a Bruker AM-400 spectrometer at 100 MHz. Infrared (IR) spectra were taken on a JASCO A 202 spectrometer. Low-resolution mass spectra were recorded with a Hitachi RMU-6MG machine (70 or 15 eV); milli-mass and SIMS (secondary ion mass spectrometer) spectra were obtained with a Hitachi M-80A spectrometer. Thin layer chromatography (TLC) analyses were performed on commercial glass plates coated with Merck Silica gel 60 F_{254} in a 0.25 mm thick layer. Preparative TLC plates were prepared using Merck Kieselgel 60 PF_{254}. Flash column chromatography was carried out with Wakogel C-200 (Wako) or BM-200 (Fuji Davison) using a medium-pressure air pump (Iwaki AP-115AN). Lobar LiChroprep RP-8 (Merck) chromatography was performed with a Perista mini-pump (Atto). High performance liquid chromatography (HPLC) was done on a Waters μBondapak C_{18} (13 mm × 11.5 cm), using a Waters pump (model 6000A) and a Waters detector (model 440 spectrometer, set at 254 nm). Acetonitrile–ammonium formate buffer (pH 3.5) (1 : 4, v/v) was used as an eluent (flow rate 1.0 ml/min). The ultraviolet (UV) irradiation experiments were carried out with a high-pressure mercury lamp apparatus (UVL-100P, Riko Kagaku Sangyo) and a Pyrex glass reaction vessel. THF and diethyl ether were distilled before use from sodium-benzophenone. Dichloromethane and DMF were distilled over calcium hydride.

Ethyl 4-Thiazoleacetate (1)——Jones *et al.*[5] reported the synthesis of ethyl 4-thiazoleacetate from ethyl γ-bromoacetoacetate in 25% yield. The exchange of the starting material, ethyl γ-bromoacetoacetate for ethyl γ-chloroacetoacetate gave an improved yield. Thus, thioformamide[10] (35.3 g, 0.58 mol), prepared from formamide (93 ml) and phosphorus pentasulfide (50 g), was added to a solution of ethyl γ-chloroacetoacetate (70.9 ml, 0.52 mol) in ethanol (100 ml) at room temperature, and then the mixture was refluxed for 20 min. After removal of the resulting salt by filtration, the filtrate was concentrated and then acidified with 2 N hydrochloric acid (200 ml) followed by washing with diethyl ether (200 ml). The aqueous layer was neutralized with saturated aqueous sodium hydrogen carbonate, and then extracted with diethyl ether. The ethereal layer was dried over sodium sulfate, and concentrated to give a residual oil, which was distilled under reduced pressure to afford **1** (35.3 g, 40%) as a colorless oil. bp 90 °C (0.3 mmHg) [lit.[5] 122 °C (15 mmHg)]. ^{1}H-NMR ($CDCl_3$) δ: 1.27 (3H, t, J=7.2 Hz), 3.89 (2H, s), 4.20 (2H, q, J=7.2 Hz), 7.26 (1H, d, J=1.0 Hz), 8.77 (1H, d, J=1.0 Hz). MS *m/z* (relative intensity, %): 172 (M^++1, 11), 171 (M^+, 17), 126 (11), 99 (54), 98 (91), 72 (11), 71 (44), 45 (46), 29 (100).

Ethyl 3-Oxo-2-(thiazol-4-yl)propanoate (2)——A solution of **1** (30 g, 0.18 mol) in DMF (30 ml) and ethyl formate (34 ml) were added to a suspension of sodium hydride (18.5 g, 0.38 mol, in 50% oil, washed three times with hexane) in DMF (300 ml). The reaction mixture was stirred at room temperature for 2 h, then poured into saturated aqueous ammonium chloride and adjusted to pH 3—4. Extraction with diethyl ether and usual work-up gave **2**[6] (34.5 g, 98%). mp 34—35 °C. IR (neat): 3175, 3125, 1710, 1620, 1280, 1230, 1200, 1010, 820 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.35 (3H, t, J=7.0 Hz), 4.28 (2H, q, J=7.0 Hz), 8.05 (1H, d, J=2.2 Hz), 8.09 (1H, s), 8.83 (1H, d, J=2.2 Hz). MS *m/z* (relative intensity, %): 199 (M^+, 22), 153 (46), 125 (100), 98 (19), 97 (34), 71 (19), 70 (18), 69 (17), 45 (24). *Anal.* Calcd for $C_8H_9NO_3S$: C, 48.23; H, 4.55; N, 7.03; S, 16.09. Found: C, 48.12; H, 4.52; N, 6.90; S, 16.15.

Ethyl (*E*)-3-Chloro-2-(thiazol-4-yl)propenoate (3-(*E*))——A solution of **2** (6.3 g, 31 mmol) in ethyl acetate (30 ml) was added to Vilsmeier reagent [prepared from phosphorus oxychloride (3.3 ml, 36 mmol) and DMF (3.5 ml, 45 mmol)] at 0 °C. The reaction mixture was stirred for 2.5 h, neutralized with 1 N sodium hydroxide, extracted with ethyl acetate, and washed with brine. The organic layer was dried over magnesium sulfate and concentrated *in vacuo*.

The residue was subjected to silica gel column chromatography (ether : hexane = 1 : 1) to give **3**-(*E*) (6.8 g, 99%) as a yellowish oil. IR (neat): 1720, 1610, 1245, 1215, 1135, 1035, 740 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.31 (3H, t, J = 7.5 Hz), 4.29 (2H, q, J = 7.5 Hz), 7.62 (1H, s), 7.63 (1H, d, J = 2 Hz), 8.87 (1H, d, J = 2 Hz). MS m/z (relative intensity, %): 219 (M^+ + 2, 16), 217 (M^+, 42), 182 (100), 172 (28), 154 (38), 146 (20), 144 (54), 117 (19), 110 (73), 82 (28), 73 (38). ^{13}C-NMR ($CDCl_3$): 14.0, 61.5, 120.2, 130.2, 133.9, 147.1, 151.7, 164.2 ppm. *Anal.* Calcd for $C_8H_8ClNO_2S$: C, 44.14; H, 3.70; Cl, 16.29; N, 6.43; S, 14.73. Found: C, 43.90; H, 3.69; Cl, 16.10; N, 6.49; S, 14.43.

Ethyl (*Z*)-3-Chloro-2-(thiazol-4-yl)propenoate (3-(*Z*))——Phosphorus oxychloride (4.68 ml, 30 mmol) was added to a solution of **2** (4.8 g, 24 mmol) in DMF (30 ml), and the mixture was heated at 100 °C for 1 h. After cooling of the reaction mixture, it was neutralized with 1 N sodium hydroxide, extracted with ethyl acetate, and washed with brine. The organic layer was dried over magnesium sulfate and concentrated *in vacuo*. The residue was subjected to silica gel column chromatography (ether : hexane = 1 : 4 to 1 : 1) to give **3**-(*Z*) (0.56 g, 11%) and **3**-(*E*) (3.8 g, 72%). **3**-(*Z*): IR (neat): 1720, 1600, 1210, 1015, 840 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.40 (3H, t, J = 7.5 Hz), 4.42 (2H, q, J = 7.5 Hz), 7.38 (1H, d, J = 2 Hz), 7.47 (1H, s), 8.75 (1H, d, J = 2 Hz). MS m/z (relative intensity, %): 219 (M^+ + 2, 13), 217 (M^+, 37), 182 (100), 172 (32), 154 (35), 146 (60), 110 (84), 82 (34), 73 (49), 29 (50). ^{13}C-NMR ($CDCl_3$): 14.1, 61.7, 115.8, 125.5, 130.9, 149.4, 153.1, 165.1 ppm. *Anal.* Calcd for $C_8H_8ClNO_2S$: C, 44.14; H, 3.70; Cl, 16.29; N, 6.43; S, 14.73. Found: C, 44.25; H, 3.83; Cl, 16.40; N, 6.43; S, 14.62.

According to the reported procedure,[4a] *tert*-butyl nitrite (245 mg, 2.46 mmol) was added to a solution of ethyl (*Z*)-3-chloro-2-(2-aminothiazol-4-yl)propenoate[2a] (191 mg, 0.82 mmol) in THF (5 ml). The mixture was stirred at 50 °C for 30 min. The desired **3**-(*Z*) was not obtained after the usual work-up.

(*E*)-3-Chloro-2-(thiazol-4-yl)propenoic Acid (4-(*E*))——A solution of potassium hydroxide (1.4 g, 25 mmol) in water (25 ml) was added to a solution of **3**-(*E*) (1.9 g, 8.5 mmol) in THF (50 ml) at 0 °C. After being stirred at room temperature for 40 min, the reaction mixture was washed with diethyl ether, acidified with 20% hydrochloric acid (pH 2), extracted with ethyl acetate, washed with brine and dried over magnesium sulfate. Concentration *in vacuo* gave **4**-(*E*) (1.5 g, 96%), which was recrystallized from a mixture of ethyl acetate and ethanol to give colorless needles. mp 117—118 °C (dec.). IR (KBr): 1695, 1585, 1515, 1485, 1420, 1305, 1250, 1195, 1020, 860, 775, 690 cm^{-1}. ^{1}H-NMR (acetone-d_6) δ: 7.78 (1H, s), 8.08 (1H, d, J = 1.9 Hz), 9.15 (1H, d, J = 1.9 Hz). ^{13}C-NMR (acetone-d_6): 122.4, 131.0, 135.2, 148.5, 154.2, 165.8 ppm. MS m/z (relative intensity, %): 189 (M^+, 3), 147 (4), 145 (13), 112 (5), 111 (7), 110 (100), 83 (10), 82 (10), 81 (7), 73 (12), 45 (10), 39 (10), 38 (5). *Anal.* Calcd for $C_6H_4ClNO_2S$: C, 38.01; H, 2.13; Cl, 18.70; N, 7.39; S, 16.91. Found: C, 38.04; H, 2.12; Cl, 18.77; N, 7.11; S, 16.90.

A solution of potassium hydroxide (0.23 g, 4.1 mmol) in water (3 ml) was added to a solution of **3**-(*Z*) (200 mg, 0.92 mmol) in THF (3 ml) at 0 °C. After the same procedure as described for the preparation of **4**-(*E*), **4**-(*E*) was isolated as the sole product.

(*Z*)-3-Chloro-2-(thiazol-4-yl)propenoic Acid (4-(*Z*))——An acetone-d_6 solution of **4**-(*E*) in an NMR tube was irradiated with a high-pressure mercury lamp for 1 h under cooling at 0 °C. ^{1}H-NMR and ^{13}C-NMR spectra were measured. They revealed that the irradiated solution consisted of a mixture of **4**-(*Z*) and **4**-(*E*) (*ca.* 1 : 2). ^{1}H-NMR (acetone-d_6) δ: 7.46 (1H, s), 7.67 (1H, d, J = 1.9 Hz), 9.13 (1H, d, J = 1.9 Hz). ^{13}C-NMR (acetone-d_6): 118.0, 124.1, 133.7, 150.6, 155.8, 166.8 ppm.

Sodium 7-[(*Z*)- and (*E*)-3-Chloro-2-(thiazol-4-yl)propenamido]-3-vinyl-3-cephem-4-carboxylate (7a and 8a)——A suspension of **4**-(*E*) (657 mg, 3.5 mmol) in acetone (60 ml) was irradiated with a high-pressure mercury lamp for 1 h under a stream of argon. After concentration of the reaction mixture *in vacuo*, the residue was dissolved in THF (10 ml). To this solution were added *p*-methoxybenzyl 7-amino-3-vinyl-3-cephem-4-carboxylate (**5a**)[11] (1.0 g, 2.9 mmol), HOBT (1-hydroxybenzotriazole) hydrate (585 mg, 4.3 mmol) and DCC (893 mg, 4.3 mmol), and the resulting mixture was stirred at room temperature for 1 h. Usual work-up and silica gel column chromatography (dichloromethane : diethyl ether = 12 : 1) gave the acylated product **6** (560 mg), which was treated with trifluoroacetic acid (3 ml) in a mixture of anisole (4 ml) and dichloromethane (8 ml) at 0 °C for 2 h. After concentration of the reaction mixture, the residue was neutralized with aqueous sodium hydrogen carbonate followed by washing with ethyl acetate, then subjected to reversed-phase silica gel column chromatography (Lobar RP-8 column). Lyophilization of the more polar eluate gave sodium 7-[(*Z*)-3-chloro-2-(thiazol-4-yl)propenamido]-3-vinyl-3-cephem-4-carboxylate (**7a**) (109 mg, 11% based on the starting material **5a**), and sodium 7-[(*E*)-3-chloro-2-(thiazol-4-yl)propenamido]-3-vinyl-3-cephem-4-carboxylate (**8a**) (136 mg, 9%) was obtained from the less polar eluate, each as an amorphous solid.

7a: IR (KBr): 1760, 1665, 1610, 1540, 1410, 1390, 1355, 1300, 1170, 820 cm^{-1}. ^{1}H-NMR (D_2O) δ: 3.47 (1H, ABd, J = 17.2 Hz), 3.57 (1H, ABd, J = 17.2 Hz), 5.07 (1H, d, J = 4.6 Hz), 5.15 (1H, d, J = 11.5 Hz), 5.30 (1H, d, J = 17.1 Hz), 5.62 (1H, d, J = 4.6 Hz), 6.64 (1H, dd, J = 17.1 and 11.5 Hz), 7.31 (1H, s), 7.90 (1H, d, J = 1.2 Hz), 8.94 (1H, d, J = 1.2 Hz). MS (SIMS) m/z: 420 (M^+ + 1).

8a: IR (KBr): 1760, 1690, 1680, 1615, 1510, 1420, 1390, 1350, 1335, 1270, 1255, 1200, 1180 cm^{-1}. ^{1}H-NMR (D_2O) δ: 3.49 (1H, ABd, J = 17.5 Hz), 3.61 (1H, ABd, J = 17.5 Hz), 5.11 (1H, d, J = 4.7 Hz), 5.15 (1H, d, J = 11.3 Hz), 5.30 (1H, d, J = 4.7 Hz), 5.32 (1H, d, J = 17.6 Hz), 6.55 (1H, dd, J = 17.6 and 11.3 Hz), 7.58 (1H, d, J = 2.0 Hz), 7.73 (1H, s), 8.89 (1H, d, J = 2.0 Hz).

Sodium 7-[(*Z*)- and (*E*)-3-Chloro-2-(thiazol-4-yl)propenamido]-3-[(1-methyl-1*H*-tetrazol-5-yl)thiomethyl]-3-

cephem-4-carboxylate (7b and 8b)——The same photoisomerization procedure was carried out with **4**-(*E*) (1.1 g, 5.7 mmol). Condensation with diphenylmethyl 7-amino-3-[(1-methyl-1*H*-tetrazol-5-yl)thiomethyl]-3-cephem-4-carboxylate (**5b**) (1 g, 2 mmol) using DCC (1.4 g, 6.8 mmol) in THF (40 ml) for 2 h, and the subsequent silica gel chromatography (ether acetate : hexane = 1 : 1) gave the acylated product (2.1 g, 55%). This product (450 mg) was treated with trifluoroacetic acid for 2 h. The same purification procedure as described for **7a** and **8a** gave **7b** (39 mg, 12%) and **8b** (28 mg, 8%), each as an amorphous solid.

7b: IR (KBr): 1765, 1670, 1605, 1390, 1300, 1290, 1240, 1175, 1105 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 3.3—3.7 (2H, m), 3.93 (3H, s), 4.28 (1H, ABd, J = 12 Hz), 4.43 (1H, ABd, J = 12 Hz), 5.05 (1H, d, J = 5 Hz), 5.65 (1H, dd, J = 7.5 and 5 Hz), 7.29 (1H, s), 7.55 (1H, d, J = 2 Hz), 9.17 (1H, d, J = 2 Hz), 9.58 (1H, d, J = 7.5 Hz, NH).

8b: IR (KBr): 1765, 1670, 1605, 1390, 1360, 1280, 1240, 1170, 1100 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 3.3—3.7 (2H, m), 3.93 (1H, s), 4.28 (1H, ABd, J = 12 Hz), 4.43 (1H, ABd, J = 12 Hz), 5.03 (1H, d, J = 5 Hz), 5.67 (1H, dd, J = 7.5 and 5 Hz), 7.39 (1H, s), 8.20 (1H, d, J = 2 Hz), 9.25 (1H, d, J = 2 Hz), 9.35 (1H, d, J = 7.5 Hz, NH).

Sodium 3-Acetoxymethyl-7-[(*Z*)- and (*E*)-3-chloro-2-(thiazol-4-yl)propenamido]-3-cephem-4-carboxylate (7c and 8c)——THF (2.6 ml) and **4**-(*E*) (500 mg, 2.6 mmol) were added to Vilsmeier reagent [prepared from phosphorus oxychloride (0.25 ml, 2.6 mmol) and DMF (0.39 ml, 5.3 mmol)] at 0 °C. The resulting mixture was heated at 40 °C for 1.5 h. In parallel, a suspension of 7-aminocephalosporanic acid **5c** (481 mg, 1.8 mmol) in a mixture of water (2.6 ml) and acetone (2.6 ml) was adjusted to pH 8.5 with saturated aqueous sodium hydrogen carbonate. To this solution, the above activated carboxylic acid solution was added dropwise at 0 °C, adjusting the reaction mixture to pH 7. The mixture was stirred at room temperature for 1 h, then the organic solvent was removed under reduced pressure, and the pH value was adjusted again to 7. Chromatography on a Lobar RP-8 column and lyophilization gave **7c** (123 mg, 15%) and **8c** (316 mg, 38%), each as a colorless amorphous solid.

7c: IR (KBr): 1765, 1660, 1605, 1540, 1400, 1350, 1230, 1070, 960 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.00 (3H, s), 3.20 (1H, ABd, J = 17.2 Hz), 3.47 (1H, ABd, J = 17.2 Hz), 4.73 (1H, ABd, J = 12.0 Hz), 4.97 (1H, ABd, J = 12.0 Hz), 5.06 (1H, d, J = 4.7 Hz), 5.63 (1H, dd, J = 7.9 and 4.7 Hz), 7.27 (1H, s), 7.53 (1H, d, J = 1.8 Hz), 9.16 (1H, d, J = 1.8 Hz), 9.62 (1H, d, J = 7.9 Hz).

8c: IR (KBr): 1765, 1670, 1610, 1540, 1400, 1350, 1235, 1035 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.00 (3H, s), 3.49 (1H, ABd, J = 17.5 Hz), 3.24 (1H, ABd, J = 17.5 Hz), 4.80 (1H, ABd, J = 11.9 Hz), 5.00 (1H, ABd, J = 11.9 Hz), 5.04 (1H, d, J = 4.8 Hz), 5.63 (1H, dd, J = 8.6 and 4.8 Hz), 7.38 (1H, s), 8.11 (1H, d, J = 2.0 Hz), 9.24 (1H, d, J = 2.0 Hz), 9.37 (1H, d, J = 8.6 Hz). MS (SIMS) m/z: 466 ($M^+ + 1$).

Sodium 7-[(*Z*)- and (*E*)-3-Chloro-2-(thiazol-4-yl)propenamido]-3-[(3-methyl-1,2,4-thiadiazol-5-yl)thiomethyl]-3-cephem-4-carboxylate (7d and 8d)——The same procedure as described for **7c** and **8c** was applied to **4**-(*E*) (250 mg, 1.3 mmol) and 7-amino-3-[(3-methyl-1,2,4-thiadiazol-5-yl)thiomethyl]-3-cephem-4-carboxylic acid **5d**[2a] (305 mg, 0.89 mmol) to afford **7d** (58 mg, 13%) and **8d** (70 mg, 35%), each as a colorless amorphous solid.

7d: IR (KBr): 1765, 1670, 1605, 1400, 1360, 1290, 1260—1000 (br), 960 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.51 (3H, s), 3.32 (1H, ABd, J = 17.3 Hz), 3.57 (1H, ABd, J = 17.3 Hz), 4.35 (1H, ABd, J = 12.3 Hz), 4.56 (1H, ABd, J = 12.3 Hz), 5.06 (1H, d, J = 4.8 Hz), 5.64 (1H, dd, J = 8.0 and 4.8 Hz), 7.26 (1H, s), 7.51 (1H, d, J = 1.9 Hz), 9.15 (1H, d, J = 1.9 Hz), 9.63 (1H, d, J = 8.0 Hz).

8d: IR (KBr): 1765, 1670, 1610, 1540, 1490, 1400, 1360, 1290, 1050, 825 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.51 (3H, s), 3.33 (1H, ABd, J = 17.1 Hz), 3.64 (1H, ABd, J = 17.1 Hz), 4.42 (1H, ABd, J = 12.5 Hz), 4.63 (1H, ABd, J = 12.5 Hz), 5.02 (1H, d, J = 4.8 Hz), 5.63 (1H, dd, J = 8.4 and 4.8 Hz), 7.35 (1H, s), 8.09 (1H, d, J = 1.9 Hz), 9.22 (1H, d, J = 1.9 Hz), 9.34 (1H, d, J = 8.4 Hz).

Sodium 7-[(*Z*)- and (*E*)-3-Chloro-2-(thiazol-4-yl)propenamido]-3-methyl-3-cephem-4-carboxylate (7e and 8e)——The same procedure as described for **7c** and **8c** was applied to **4**-(*E*) (250 mg, 1.3 mmol) and 7-amino-3-methyl-3-cephem-4-carboxylic acid (**5e**) (191 mg, 0.89 mmol) to afford **7e** (55 mg, 15%) and **8e** (232 mg, 64%), each as a colorless amorphous solid.

7e: IR (KBr): 1760, 1670, 1600, 1540, 1410, 1360, 1285, 1260—1000 (br), 820 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.90 (3H, s), 3.08 (1H, ABd, J = 17.1 Hz), 3.38 (1H, ABd, J = 17.1 Hz), 4.99 (1H, d, J = 4.6 Hz), 5.55 (1H, dd, J = 8.1 and 4.8 Hz), 7.26 (1H, s), 7.52 (1H, d, J = 1.8 Hz), 9.15 (1H, d, J = 1.8 Hz), 9.52 (1H, d, J = 8.5 Hz). MS (SIMS) m/z: 408 ($M^+ + 1$).

8e: IR (KBr): 1760, 1670, 1600, 1540, 1410, 1370, 1285, 1220—1000 (br), 825 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.91 (3H, s), 3.10 (1H, ABd, J = 17.6 Hz), 3.46 (1H, ABd, J = 17.6 Hz), 4.96 (1H, d, J = 4.7 Hz), 5.53 (1H, dd, J = 8.5 and 4.7 Hz), 7.38 (1H, s), 8.11 (1H, d, J = 1.9 Hz), 9.23 (1H, d, J = 1.9 Hz), 9.32 (1H, d, J = 8.5 Hz). MS (SIMS) m/z: 408 ($M^+ + 1$).

7-[(*Z*)- and (*E*)-3-Chloro-2-(thiazol-4-yl)propenamido]-3-(4-methoxypyridiniummethyl)-3-cephem-4-carboxylate (7f and 8f)——The same procedure as described for **7c** and **8c** was applied to **4**-(*E*) (250 mg, 1.3 mmol) and 7-amino-3-(4-methoxypyridiniummethyl)-3-cephem-4-carboxylate (**5f**) [prepared from 7-*tert*-butoxycarbonylamino-3-(4-methoxypyridiniummethyl)-3-cephem-4-carboxylate (556 mg, 1.3 mmol) by deprotection of the *tert*-butoxycarbonyl group with trifluoroacetic acid] to afford **7f** (17 mg, 3%) and **8f** (51 mg, 8%), each as a colorless amorphous solid.

7f: IR (KBr): 1775, 1670, 1640, 1610, 1570, 1525, 1400, 1360, 1320, 1210, 1160, 1060, 840 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.96 (1H, ABd, J = 17.5 Hz), 3.52 (1H, ABd, J = 17.5 Hz), 4.06 (3H, s), 4.86 (1H, ABd, J = 13.5 Hz),

5.12 (1H, d, J=4.9 Hz), 5.48 (1H, ABd, J=13.5 Hz), 5.69 (1H, dd, J=7.8 and 4.7 Hz), 7.24 (1H, s), 7.49 (1H, d, J=1.9 Hz), 7.64 (1H, d, J=7.5 Hz), 9.14 (1H, d, J=1.9 Hz), 9.30 (1H, d, J=7.5 Hz), 9.63 (1H, d, J=7.8 Hz). MS (SIMS) m/z: 493 ($M^+ + 1$).

8f: IR (KBr): 1780, 1670, 1645, 1615, 1575, 1525, 1325, 1160 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.96 (1H, ABd, J=17.5 Hz), 3.52 (1H, ABd, J=17.5 Hz), 4.10 (3H, s), 4.92 (1H, ABd, J=14.0 Hz), 5.07 (1H, d, J=4.8 Hz), 5.50 (1H, ABd, J=14.0 Hz), 5.65 (1H, dd, J=7.9 and 4.8 Hz), 7.31 (1H, s), 7.66 (1H, d, J=7.9 Hz), 8.06 (1H, d, J=2.0 Hz), 9.18 (1H, d, J=2.0 Hz), 9.32 (1H, d, J=7.9 Hz). MS (SIMS) m/z: 493 ($M^+ + 1$).

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