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An Efficient Method for the Preparation of 3-(Substituted thiomethyl)-7-aminocephalosporins

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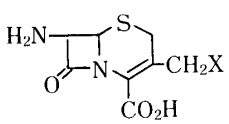
A practical method to prepare 7-amino-3-(substituted thiomethyl)-3-cephem-4-carboxylic acids (**1**) was developed. The acetoxy group of 3-acetoxymethyl-7-amino-3-cephem-4-carboxylic acid (7-ACA, **2**) was displaced by various thiols in the presence of strong acids (including Lewis acids) under nonaqueous conditions to afford **1** in high yields. Similar substitution of the Δ^2-isomers of **2** was achieved by the same method.

Keywords——β-lactam antibiotics; cephem; 3-acetoxymethyl-7-amino-3(or 2)-cephem-4-carboxylic acid; 7-amino-3-(substituted thiomethyl)-3(or 2)-cephem-4-carboxylic acid; substitution; thiol; strong acid; Lewis acid

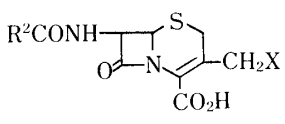
In the development of various β-lactam antibiotics, remarkable progress has been achieved in the field of cephems, and many of them are already in clinical use.[1] 7-Amino-3-(substituted thiomethyl)-3-cephem-4-carboxylic acids (**1**) are important intermediates for the preparation of cephem derivatives.[2]

Two methods are known for the preparation of **1**: (a) treatment of 3-acetoxymethyl-7-amino-3-cephem-4-carboxylic acid (7-ACA, **2**) with thiols in an aqueous solution under neutral or mildly basic conditions with heating,[3] and (b) treatment of acyl derivatives (**3**) of **2** with thiols similarly,[3] followed by removal of the acyl side chains in the substituted products (**4**).[4] The yields of the substituted products ranged from 40 to 70%. The low yields may be mainly due to the instability of the cephem nucleus in aqueous solution. Therefore, it was expected that the yield would be improved if the substitution reaction could be performed under nonaqueous conditions.

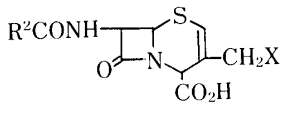
Peter *et al.* reported that the reaction of 3-acetoxymethyl-7-acylamino-2-cephem-4-carboxylic acids (**5**) with thiols in trifluoroacetic acid, followed by the usual oxidative-reductive isomerization procedure[5] afforded the Δ^3-isomer (**4**).[6] It has also been observed that the conventional substitution reaction in an aqueous solution took place in a shorter time with **2** than with the acyl derivatives (**3**).[3]



1: X=SR^1
2: X=OCOCH$_3$



3: X=OCOCH$_3$
4: X=SR^1

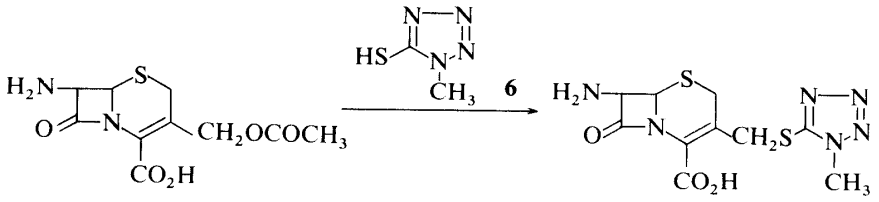


5: X=OCOCH$_3$

Fig. 1

Based on these findings, we investigated the substitution reaction of **2** under nonaqueous conditions. The acetate (**2**) is sparingly soluble in most organic solvents, but it became soluble on adding *p*-toluenesulfonic acid in acetic acid. 5-Mercapto-1-methyl-1*H*-tetrazole (**6**) was

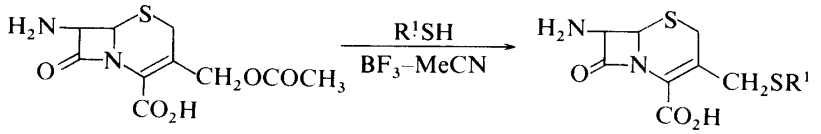
TABLE I. The Substitution of 7-ACA (**2**) with 5-Mercapto-1-methyl-1*H*-tetrazole (**6**)



2 **1a**

Acid	Molar ratio Acid/**2**	Solvent	Temp. (°C)	Time (h)	Yield (%)
BF_3	3.0	MeCN	30	1.5	94.7
$BF_3 \cdot (C_2H_5)_2O$	3.0	MeCN	50	2.0	91.5
$BF_3 \cdot (C_4H_9)_2O$	3.0	MeCN	50	2.0	88.7
$BF_3 \cdot AcOH$	4.0	MeCN	50	2.0	82.5
$SnCl_4$	3.0	AcOH	50	1.5	75.0
$ZnCl_2$	10.0	AcOH	50	4.0	76.2
F_3CSO_3H	3.0	MeCN	30	1.5	92.0
FSO_3H	3.0	MeCN	30	1.0	82.4
H_2SO_4	10.0	MeCN	30	1.0	89.0
CH_3SO_3H	6.0	AcOH	50	2.5	82.3
$HClO_4$	4.0	AcOH	50	2.5	80.8
$FSO_3H \cdot SbF_5$	1.5	AcOH	30	2.5	75.6

TABLE II. 7-Amino-3-(substituted thiomethyl)-3-cephem-4-carboxylic Acids (**1**)



2 **1**

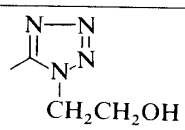
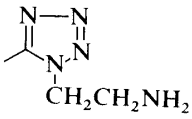
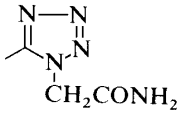
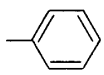
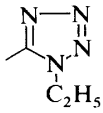
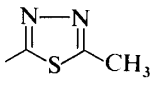
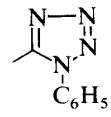
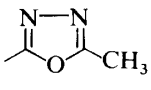
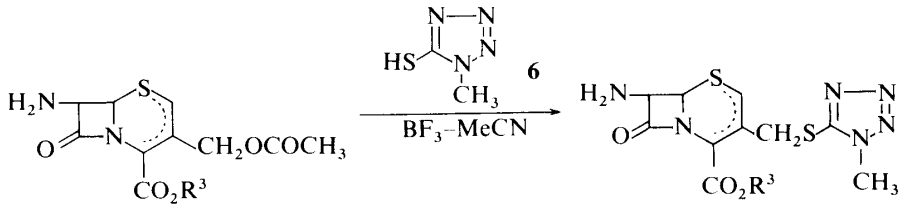
Compd. No.	R^1	Yield (%)	Compd. No.	R^1	Yield (%)
1b	$-CH_2CH_2CH_3$	84	**1h**		89
1c	$-CH_2CO_2H$	80	**1i**		79
1d	$-CH_2CO_2C_2H_5$	82	**1j**		92
1e		83	**1k**		77
1f		87	**1l**		86
1g		82	**1m**		89

TABLE III. The Substitution of the Δ^2-Isomer and Carboxylic Ester with 5-Mercapto-1-methyl-1*H*-tetrazole (**6**)



Starting material	Reaction conditions		Product	Yield (%)
	Temp. (°C)	Time (h)		
7 Δ^2, $R^3=H$	25	1.0	**8** Δ^2, $R^3=H$	90.3
9 Δ^3, $R^3=C_2H_5$	25	1.5	**11** Δ^3, $R^3=C_2H_5$	85.6
10 Δ^2, $R^3=C_2H_5$	25	0.5	**12** Δ^2, $R^3=C_2H_5$	89.1

added to the resulting salt solution and then the mixture was warmed to give the substituted product (**1a**). Various acids were tried in order to improve the yield. The reaction conditions which gave the substituted product (**1a**) in high yields are summarized in Table I. The reaction proceeded smoothly under relatively mild conditions (30 °C, 1.5 h), and **1a** was obtained in high yield, by treatment of **2** with 3 mol eq of boron trifluoride (BF_3) in acetonitrile. The polar solvents such as acetic acid, acetonitrile, nitromethane and sulfolane were preferable and **2** dissolved rapidly in these solvents on adding strong acids (including Lewis acids).

The reaction of other various thiols with **2** was investigated in acetonitrile by employing BF_3. Substituted products (**1b**—**m**) were obtained in high yields as shown in Table II.

3-Acetoxymethyl-7-amino-2-cephem-4-carboxylic acid (**7**) and **6** were reacted in the presence of BF_3 in acetonitrile in order to assess the difference in reactivity between Δ^3-cephem and Δ^2-cephem. The reaction of Δ^2-cephem proceeded more rapidly than that of Δ^3-isomer (**2**) to afford the substituted product (**8**) in high yield. The acetoxy group of the carboxylic esters (**9**, **10**) was also displaced easily by **6** under the same conditions. The reaction conditions and yields are shown in Table III.

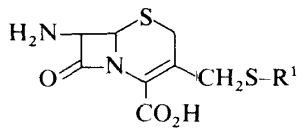
It seems that the substitution reaction proceeds smoothly owing to a decrease of the nucleophilicity of the amino group at C-7 and an acceleration of the elimination of the acetoxy group through coordination of a strong acid to **2**.

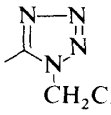
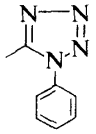
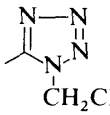
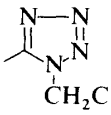
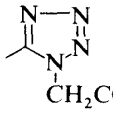
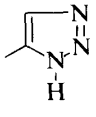
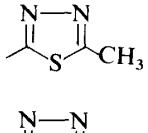
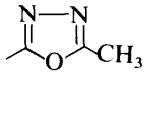
Experimental

All melting points are uncorrected. Infrared (IR) spectra were measured on a Hitachi 215 spectrophotometer. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded with a Hitachi R-24 spectrometer using tetramethylsilane (TMS) as an internal standard. Abbreviations are as follows: s = singlet, d = doublet, t = triplet, q = quartet and m = multiplet.

7-Amino-3-(substituted thiomethyl)-3-cephem-4-carboxylic Acids (1)——Typical Procedure: First, 5.12 g of 5-mercapto-1-methyl-1*H*-tetrazole (**6**) and 12.0 g of 3-acetoxymethyl-7-amino-3-cephem-4-carboxylic acid (**2**: 7-ACA) were successively added to a stirred solution of boron trifluoride (9.0 g) in 60 ml of anhydrous MeCN. The resulting solution was allowed to react at 30 °C for 90 min. After cooling in an ice-bath, the reaction solution was diluted with 60 ml of H_2O and adjusted to pH 4.0 by the addition of 28% NH_4OH. Crystals that precipitated were collected by filtration, and washed with H_2O and then Me_2CO, to give 13.7 g (94.7%) of 7-amino-3-(1-methyl-1*H*-tetrazol-5-yl)thiomethyl-3-cephem-4-carboxylic acid (**1a**). mp 224—226 °C (dec.). IR ν_{max}^{KBr} cm^{-1}: 1792, 1610 (C=O). ^{1}H-NMR (F_3CCO_2D–D_2O) δ: 3.58 (2H, s, C_2-H_2), 3.84 (3H, s, N-CH_3), 4.09 (2H, s, C_3-CH_2), 4.91 (1H, d, J = 5 Hz, C_6-H), 5.05

TABLE IV. Physical Properties of 7-Amino-3-(substituted thiomethyl)-3-cephem-4-carboxylic Acids (**1**)



Compd. No.	R^1	mp (dec.) (°C)	IR ν_{max}^{KBr} cm^{-1} (C=O)	^{1}H-NMR (F_3CCO_2D-D_2O) δ
1b	$-CH_2CH_2CH_3$	215	1795 1610	0.95 (3H, t, J=7 Hz, CH_3), 1.59 (2H, m, $CH_2C\underline{H}_2CH_3$), 2.52 (2H, t, J=7 Hz, $C\underline{H}_2C_2H_5$), 3.66 (2H, s, C_2-H_2), 3.77 (2H, s, C_3-CH_2), 5.10 (1H, d, J=5 Hz, C_6-H), 5.27 (1H, d, J=5 Hz, C_7-H)
1c	$-CH_2CO_2H$	193—196	1775 1695 1610	3.41 (2H, s, $C\underline{H}_2CO_2H$), 3.71 (2H, s, C_2-H_2), 3.59, 4.04 (2H, ABq, J=14 Hz, C_3-CH_2), 5.10 (1H, d, J=5 Hz, C_6-H), 5.25 (1H, d, J=5 Hz, C_7-H)
1d	$-CH_2CO_2C_2H_5$	208—210	1800 1715 1610	1.29 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 3.41 (2H, s, $C\underline{H}_2CO_2C_2H_5$), 3.74 (2H, s, C_3-CH_2), 3.73, 4.01 (2H, ABq, J=14 Hz, C_3-CH_2), 4.20 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$), 5.16 (1H, d, J=5 Hz, C_6-H), 5.33 (1H, d, J=5 Hz, C_7-H)
1e		235	1785 1610	3.52 (2H, s, C_2-H_2), 3.79, 4.35 (2H, ABq, J=14 Hz, C_3-CH_2), 5.01 (2H, m, C_6-H, C_7-H), 7.30 (5H, m, C_6H_5)
1f		201—203	1785 1610	1.55 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 3.81 (2H, s, C_2-H_2), 4.35 (2H, s, C_3-CH_2), 4.42 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$), 5.15 (1H, d, J=5 Hz, C_6-H), 5.28 (1H, d, J=5 Hz, C_7-H)
1g		209—210	1800 1610	3.75 (2H, s, C_2-H_2), 4.35, 4.61 (2H, ABq, J=14 Hz, C_3-CH_2), 5.20 (2H, m, C_6-H, C_7-H), 7.58 (5H, s, C_6H_5)
1h		190—192	1795 1610	3.89 (2H, s, C_2-H_2), 4.12 (2H, t, J=5 Hz, $C\underline{H}_2OH$), 4.48 (2H, s, C_3-CH_2), 4.67 (2H, t, J=5 Hz, N-CH_2), 5.30 (1H, d, J=5 Hz, C_6-H), 5.37 (1H, d, J=5 Hz, C_7-H)
1i		204—207	1790 1610	3.67 (2H, t, J=6 Hz, $C\underline{H}_2NH_2$), 3.80 (2H, s, C_2-H_2), 4.29, 4.31 (2H, ABq, J=14 Hz, C_3-CH_2), 4.80 (2H, t, J=6 Hz, N-CH_2), 5.13 (1H, d, J=5 Hz, C_6-H), 5.26 (1H, d, J=5 Hz, C_7-H)
1j		189—191	1790 1680 1610	3.73 (2H, s, C_2-H_2), 4.28, 4.37 (2H, ABq, J=14 Hz, C_3-CH_2), 5.03—5.23 (4H, m, N-CH_2, C_6-H, C_7-H)
1k		209	1800 1610	3.79 (2H, s, C_2-H_2), 3.81, 4.32 (2H, ABq, J=14 Hz, C_3-CH_2), 5.15 (1H, d, J=5 Hz, C_6-H), 5.28 (1H, d, J=5 Hz, C_7-H), 8.28 (1H, s, CH in triazole)
1l		205—207	1790 1610	2.88 (3H, s, CH_3), 3.75 (2H, s, C_2-H_2), 4.33, 4.61 (2H, ABq, J=14 Hz, C_3-CH_2), 5.20 (2H, m, C_6-H, C_7-H)
1m		206—207	1795 1610	2.59 (3H, s, CH_3), 3.80 (2H, s, C_2-H_2), 4.37 (2H, s, C_3-CH_2), 5.19 (1H, d, J=5 Hz, C_6-H), 5.32 (1H, d, J=5 Hz, C_7-H)

(1H, d, $J=5$ Hz, C_7-H). *Anal.* Calcd for $C_{10}H_{12}N_6O_3S_2$: C, 36.59; H, 3.69; N, 25.61. Found: C, 36.54; H, 3.65; N, 25.21. The above reaction solution was treated with 7.3 ml of 35% HCl and stirred at room temperature for 2 h. The precipitated solid was filtered and washed with Me_2CO to give 14.1 g (87.7%) of **1a**·hydrochloride as colorless needles. mp 184—186 °C (dec.). IR ν_{max}^{KBr} cm^{-1}: 1770, 1710 (C=O). *Anal.* Calcd for $C_{10}H_{13}ClN_6O_3S_2$: C, 32.91; H, 5.39; N, 23.03. Found: C, 32.41; H, 5.37; N, 22.71.

In a similar manner, 7-ACA (**2**) was allowed to react with **6** by using other strong acids (Lewis acids) instead of boron trifluoride, to afford **1a**. The reaction conditions and the yields are listed in Table I.

Other thiols were allowed to react with 7-ACA (**2**) in the presence of boron trifluoride in MeCN under the conditions of the typical procedure to afford 7-amino-3-(substituted thiomethyl)-3-cephem-4-carboxylic acids (**1b**—**m**). The yields and the spectral data are listed in Tables II and IV, respectively.

7-Amino-3-(1-methyl-1*H*-tetrazol-5-yl)thiomethyl-2-cephem-4-carboxylic Acid Dihydrate (8·2H_2O)——3-Acetoxymethyl-7-amino-2-cephem-4-carboxylic acid (**7**) (0.53 g) and **6** (0.23 g) were added to a solution of boron trifluoride (0.40 g) in MeCN (5.3 ml). After being stirred at 25 °C for 1 h, the reaction solution was concentrated under reduced pressure. The residual oil was dissolved in 8 ml of 50% aqueous MeOH and the solution was adjusted to pH 4 with 28% NH_4OH, then stirred at 5 °C for 2 h. The resulting crystals were collected to give **8**·2H_2O (0.64 g, 90.3%) as colorless needles. mp 110—112 °C (dec.). IR ν_{max}^{KBr} cm^{-1}: 1770, 1610 (C=O). ^{1}H-NMR (F_3CCO_2D–D_2O) δ: 3.93 (3H, s, N-CH_3), 4.12 (2H, s, C_3-CH_2), 4.96 (1H, d, $J=5$ Hz, C_6-H), 5.25 (1H, s, C_4-H), 5.38 (1H, d, $J=5$ Hz, C_7-H), 6.38 (1H, s, C_2-H).

***p*-Toluenesulfonic Acid Salt of Ethyl 7-Amino-3-(1-methyl-1*H*-tetrazol-5-yl)thiomethyl-3-cephem-4-carboxylate (11·*p*-TsOH)**——The *p*-toluenesulfonic acid salt of ethyl 3-acetoxymethyl-7-amino-3-cephem-4-carboxylate (**9**·*p*-TsOH) (0.47 g) and **6** (0.12 g) were added to a solution of boron trifluoride (0.20 g) in MeCN (4.7 ml). After being stirred at 25 °C for 90 min, the reaction solution was concentrated under reduced pressure. The residue was dissolved in a mixture of CH_2Cl_2 and H_2O, and the solution was adjusted to pH 7.0 with $NaHCO_3$. The organic layer was washed with H_2O and dried over $MgSO_4$. After the addition of *p*-toluenesulfonic acid monohydrate (0.19 g), the solvent was removed under reduced pressure. The residual solid was washed with Et_2O to give 0.45 g (85.6%) of **11**·*p*-TsOH. mp 115—122 °C. IR ν_{max}^{KBr} cm^{-1}: 1790, 1715 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.23 (3H, t, $J=7$ Hz, $CH_2C\underline{H}_3$), 2.30 (3H, s, CH_3), 3.45 (2H, s, C_2-H_2), 3.81 (3H, s, N-CH_3), 4.10 (2H, q, $J=7$ Hz, $C\underline{H}_2CH_3$), 4.02, 4.30 (2H, ABq, $J=14$ Hz, C_3-CH_2), 4.95 (2H, m, C_6-H, C_7-H), 7.01, 7.59 (4H, $A_2'B_2'$, $J=9$ Hz, aromatic protons).

***p*-Toluenesulfonic Acid Salt of Ethyl 7-Amino-3-(1-methyl-1*H*-tetrazol-5-yl)thiomethyl-2-cephem-4-carboxylate (12·*p*-TsOH)**——A mixture of ethyl 3-acetoxymethyl-7-amino-2-cephem-4-carboxylate hydrochloride (**10**·HCl, 0.67 g), **6** (0.23 g) and boron trifluoride (0.40 g) in MeCN (6.7 ml) was stirred at 25 °C for 30 min. Work-up as described for **11**·*p*-TsOH gave 0.94 g (89.1%) of **12**·*p*-TsOH as colorless needles. mp 147—149 °C. IR ν_{max}^{KBr} cm^{-1}: 1790, 1730 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.22 (3H, t, $J=7$ Hz, CH_2-$C\underline{H}_3$), 2.30 (3H, s, CH_3), 3.78 (3H, s, N-CH_3), 3.95—4.25 (5H, m, C_4-H, C_3-CH_2, $C\underline{H}_2CH_3$), 4.97 (1H, d, $J=5$ Hz, C_6-H), 5.29 (1H, d, $J=5$ Hz, C_7-H), 6.23 (1H, s, C_2-H), 7.03, 7.63 (4H, $A_2'B_2'$, $J=9$ Hz, aromatic protons). *Anal.* Calcd for $C_{19}H_{24}N_6O_6S_3$: C, 43.15; H, 4.54; N, 15.90. Found: C, 43.13; H, 4.57; N, 15.84.

References

1) J. A. Webber and J. L. Ott, "Structure–Activity Relationships among the Semisynthetic Antibiotics," ed. by D. Perlman, Academic Press Inc., New York, San Francisco, London, 1977, pp. 161—233; H. Sakai, *Yuki Gosei Kagaku Kyokai Shi*, **39**, 243 (1981); H. Umezawa, *Farumashia*, **16**, 479 (1980).
2) G. V. Kaiser and S. Kukolja, "Cephalosporins and Penicillins, Chemistry and Biology," ed. by E. H. Flynn, Academic Press Inc., New York, London, 1972, pp. 83—91.
3) J. D. Cocker, B. R. Cowley, J. S. G. Cox, S. Eardley, G. I. Gregory, J. K. Lazenby, A. G. Long, J. C. P. Sly and G. A. Somerfield, *J. Chem. Soc.*, **1965**, 5015; R. M. DeMarinis, J. C. Boehm, G. L. Dunn, J. R. E. Hoover, J. V. Uri, J. R. Guarini, L. Phillips, P. Actor and J. A. Weisbach, *J. Med. Chem.*, **20**, 30 (1977); G. S. Lewis and P. H. Nelson, *ibid.*, **22**, 1214 (1979); C. F. Murphy and J. A. Webber, "Cephalosporins and Penicillins, Chemistry and Biology," ed. by E. H. Flynn, Academic Press Inc., New York, London, 1972, pp. 158—160.
4) B. Fechtig, H. Peter, H. Bickel and E. Vischer, *Helv. Chim. Acta*, **51**, 1108 (1968); D. Bormann and M. Worm, Ger. Offen. Patent 2359402 (1975) [*Chem. Abstr.*, **83**, 114439*u* (1975)].
5) G. V. Kaiser, R. D. G. Cooper, R. E. Koehler, C. F. Murphy, J. A. Webber, I. G. Wright and E. M. Van Heyningen, *J. Org. Chem.*, **35**, 2430 (1970).
6) H. Peter, B. Müller, W. Sibral and H. Bickel, Ger. Offen. Patent 2503335 (1975) [*Chem. Abstr.*, **84**, 17389*r* (1976)].