A Convenient Synthesis of C(2)-Substituted Cephalosporins

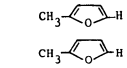
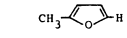
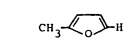
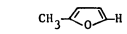
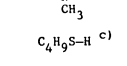
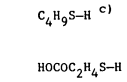
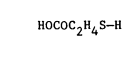
Sigeru Torii,* Hideo Tanaka, Norio Saitoh, Takashi Siroi,
Michio Sasaoka, Nobuhito Tada, and Junzo Nokami
Department of Industrial Chemistry, School of Engineering, Okayama University, Okayama 700
(Received March 3, 1983)

Synopsis. Replacement of the C(2)-substituents of 2-acetoxy- or 2-methoxycephalosporin with nucleophiles was performed efficiently in dichloromethane in the presence of acid-catalysts, affording cephalosporins bearing heteroaromatic moieties, sulfenyl, and alkoxyl groups at the C(2)-position.

Chemical modification of natural penicillins and cephalosporins has been intensively investigated in order to obtain new clinically significant drugs with greater antibacterial activity.[1] In this connection, much attention has been paid to introduction of a desired functional group to the C(2)-position of cephalosporins.[2] However, the C(2)-substituents so far introduced are only known of alkyl,[3] alkylidene,[4] and/or a few simple functional groups, *e.g.*, acetoxyl,[5] methoxyl,[6] and methylthio groups.[7]

The development of synthesis procedures of C(2)-acetoxy- and methoxycephalosporins[5,6] prompted us to investigate the replacement of the acetoxyl and methoxyl groups of **2** with more complex substituents. We now found that the replacement of the C(2)-substituents of **2** can be successfully performed by treatment with various nucleophiles in dichloromethane in the presence of an acid catalyst.

Table 1. C(2)-Substitution of 2-acetoxy- or 2-methoxycephalosporin with nucleophiles[a]

Entry	Compound 2 R	Nu-H	Acid	Temp °C	Time h	Product 4	Yield[b] %
1	CH_3CO		$TiCl_4$	-25	4	4a	87
2	CH_3CO		$AlCl_3$	3	1.5	4a	84
3	CH_3CO		p-TsOH	5	8	4a	78
4	CH_3		$AlCl_3$	25	0.6	4a	67
5	CH_3		p-TsOH	25	3	4a	67
6	CH_3		p-TsOH	25	3	4b	55
7	CH_3CO		$TiCl_4$	-30	0.2	4c	96
8	CH_3CO		$AlCl_3$	-30	1.6	4d	91
9	CH_3CO	C_4H_9S-H [c]	$TiCl_4$	-30	0.6	4e	64
10	CH_3CO	$HOCOC_2H_4S$-H [c]	$TiCl_4$	-40	3	4f	59
11	CH_3CO	 [c]	$AlCl_3$	-30	1.1	4g	90
12	CH_3CO	 [c]	$AlCl_3$	-30	2	4h	81
13	CH_3CO	 [c]	$AlCl_3$	-20	2	4i	74
14	CH_3CO	CH_2=$CHCH_2O$-H [c]	$TiCl_4$	3	3	4j	83

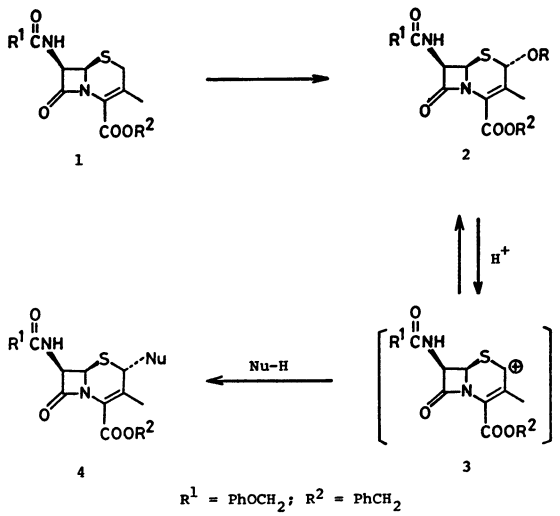
a) Unless otherwise noted, reaction was carried out according to the general procedure described in the experimental. b) Isolated yield after column chromatography (SiO_2, benzene-AcOEt). c) 1.2—1.5 molar equiv of nucleophiles were used.

The reaction conditions along with the yield of the desired products **4** are summarized in Table 1. Treatment of **2a** (R=CH_3CO) with 2-methylfuran in dichloromethane in the presence of titanium(IV) chloride at −25 °C for 25 min afforded 2-(5-methyl-2-furyl)cephalosporin **4a** in 87% yield (entry 1). Aluminum (III) chloride and *p*-toluenesulfonic acid were also effective catalysts for this transformation (entries 2 and 3). Reaction of **2b** (R=CH_3) with 2-methylfuran in the same media afforded same product **4a** (entries 4 and 5). In a similar manner, the reaction of **2a** with furan, 2-methylthiophene, and *N*-methylpyrrole afforded the corresponding C(2)-substituted cephalosporins **4b—d**. Replacement of the acetoxyl group of **2a** with sulfenyl and allyloxyl groups was performed by treatment with various thiols and allyl alcohol in dichloromethane in the presence of titanium (IV) chloride and/or aluminum (III) chloride (entries 9—14).

In the present acid-catalyzed substitution reaction, no detectable amounts of by-products resulting from the C(2)-carbon-sulfur bond fission were isolated. This suggests that in the initial stage of the reaction, selective attack of Lewis acids or proton on the acetoxyl and methoxyl groups of **2** generates cation **3**, which, in turn, reacts with the nucleophiles to give **4** (Scheme 1).

Experimental

All melting points are uncorrected. IR spectra were determined with a JASCO IRA-I infrared spectrometer. ^1H NMR spectra were obtained at 60 MHz with a Hitachi R-24 spectrometer and/or at 100 MHz with a JEOL FX-100 spectrometer. Elemental analyses were performed in our



R^1 = $PhOCH_2$; R^2 = $PhCH_2$

Scheme 1.

laboratory.

Benzyl 2-acetoxy-3-methyl-7-phenoxyacetoamido-Δ^3-cephem-4-carboxylate (**2a**) was prepared from benzyl 3-methyl-7-phenoxyacetoamido-Δ^3-cephem-4-carboxylate (**1**) as previously described:[2] mp 63—65 °C (from ether); IR ($CHCl_3$) 3450, 1790, 1745, 1730, and 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.98 (3H, s), 2.00 (3H, s), 4.40 (2H, s), 5.00 (1H, d, J=5 Hz), 5.16 (2H, s), 5.76 (1H, dd, J=5 and 9 Hz), 6.17 (1H, s), and 6.6—7.4 (11H, m).

Found: C, 60.43; H, 5.15%. Calcd for $C_{25}H_{24}N_2O_7S$: C, 60.47; H, 4.87%.

Benzyl 2-methoxy-3-methyl-7-phenoxyacetoamido-Δ^3-cephem-4-carboxylate (**2b**) was prepared from **1** in accordance with the reported procedure:[3] mp 121—122 °C (from ether); IR ($CHCl_3$) 3250, 1775, 1730, and 1675 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.14 (3H, s), 3.38 (3H, s), 4.49 (2H, s), 4.70 (1H, s), 4.96 (1H, d, J=5 Hz), 5.20 (2H, s), 5.80 (1H, dd, J=5 and 9 Hz), 6.7—7.4 (10H, m), and 7.45 (1H, d, J=9 Hz).

Found: C, 61.66; H, 5.23%. Calcd for $C_{24}H_{24}N_2O_6S$: C, 61.53; H, 5.16%.

Replacement of the C(2)-Substituents of 2-Acetoxy- or 2-Methoxycephalosporin with Nucleophiles. The reaction conditions and results are summarized in Table 1. The general procedure is exemplified by the preparation of **4a** (Nu=5-methyl-2-furyl) (entry 1 in Table 1). To a stirred solution of **2a** (34.2 mg, 0.069 mmol) and 2-methylfuran (0.5 mL, 5 mmol) in CH_2Cl_2 (0.5 mL) was added $TiCl_4$ (0.8 μL, 0.007 mmol) at −25 °C. After being stirred at −25 °C for 4 h, the reaction was quenched with two drops of an aqueous $NaHCO_3$. The mixture was diluted with CH_2Cl_2, dried over Na_2SO_4, and filtered. The filtrates were concentrated and chromatographed (SiO_2, benzene–AcOEt=20:1) to give **4a** (31.3 mg, 87%) as a colorless foam: IR ($CHCl_3$) 1782, 1724, and 1698 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.12 (3H, s), 2.28 (3H, s), 4.57 (2H, s), 4.61 (1H, s), 5.10 (1H, d, J=5 Hz), 5.35 (2H, s), 5.96 (1H, dd, J=5 and 8.4 Hz), 5.98 (2H, s), and 6.9—7.7 (11H, m).

Found: C, 64.99; H, 5.32%. Calcd for $C_{28}H_{26}N_2O_6S$: C, 64.85; H, 5.05%.

Compound **4b** (Nu=2-furyl): IR ($CHCl_3$) 1787, 1730, and 1697 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.08 (3H, s), 4.49 (2H, s), 4.58 (1H, s), 5.01 (1H, d, J=5 Hz), 5.28 (2H, s), 5.88 (1H, dd, J=5 and 9 Hz), 5.95—6.40 (2H, m), and 6.7—7.6 (12H, m).

Found: C, 64.13; H, 4.85%. Calcd for $C_{27}H_{24}N_2O_6S$: C, 64.27; H, 4.79%.

Compound **4c** (Nu=5-methyl-2-thienyl): IR ($CHCl_3$) 1783, 1725, and 1693 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.14 (3H, s), 2.44 (3H, s), 4.54 (2H, s), 4.26 (1H, s), 4.95 (1H, d, J=5.2 Hz), 5.32 (2H, s), 5.94 (1H, dd, J=5.2 and 8 Hz), 6.55 (2H, s), and 6.78—7.26 (11H, m).

Found: C, 63.14; H, 4.98%. Calcd for $C_{28}H_{26}N_2O_5S_2$: C, 62.90; H, 4.90%.

Compound **4d** (Nu=1-methyl-2-pyrrolyl): IR ($CHCl_3$) 1784, 1725, and 1698 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.07 (3H, s), 3.60 (3H, s), 4.50 (2H, s), 4.54 (1H, s), 4.80 (1H, d, J=5 Hz), 5.29 (2H, s), 5.6—6.05 (3H, m), and 6.5—7.6 (13H, m).

Found: C, 65.02; H, 5.25%. Calcd for $C_{28}H_{27}N_3O_5S$: C, 64.97; H, 5.26%.

Compound **4e** (Nu=butylthio): IR ($CHCl_3$) 1780, 1720, and 1695 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.90 (3H, m), 1.55 (4H, m), 2.22 (3H, s), 2.74 (2H, m), 4.45 (1H, s), 4.49 (2H, s), 5.30 (2H, s), 5.39 (1H, d, J=5 Hz), 6.00 (1H, dd, J=5 and 10 Hz), and 6.8—7.6 (11H, m).

Found: C, 61.65; H, 5.46%. Calcd for $C_{27}H_{30}N_2O_5S_2$: C, 61.57; H, 5.74%.

Compound **4f** (Nu=2-carboxylethylthio): IR ($CHCl_3$) 1780, 1710, and 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.18 (3H, s), 2.5—3.1 (4H, m), 4.54 (3H, s), 5.25 (2H, s), 5.32 (1H, d, J=5 Hz), 5.95 (1H, dd, J=5 and 9 Hz), and 6.7—8.6 (12H, m).

Found: C, 57.62; H, 5.13%. Calcd for $C_{26}H_{26}N_2O_7S_2$: C, 57.55; H, 4.83%.

Compound **4g** (Nu=1-phenyl-1,2,3,4-tetrazol-5-ylthio): IR ($CHCl_3$) 1795, 1735, and 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.22 (3H, s), 4.51 (2H, s), 5.06 (1H, d, J=4.2 Hz), 5.24 (2H, s), 5.87 (1H, s), 5.87 (1H, dd, J=4.2 and 8.8 Hz), and 6.7—7.7 (16H, m).

Found: C, 58.66; H, 4.40%. Calcd for $C_{30}H_{26}N_6O_5S_2$: C, 58.62; H, 4.26%.

Compound **4h** (Nu=1-methyl-1,2,3,4-tetrazol-5-ylthio): IR ($CHCl_3$) 1785, 1723, and 1692 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.26 (3H, s), 3.90 (3H, s), 4.48 (2H, s), 5.23 (1H, d, J=5 Hz), 5.27 (2H, s), 5.71 (1H, s), 5.93 (1H, dd, J=5 and 8 Hz), and 6.7—7.5 (11H, m).

Found: C, 54.57; H, 4.56%. Calcd for $C_{25}H_{24}N_6O_5S_2$: C, 54.33; H, 4.38%.

Compound **4i** (Nu=5-methyl-1,3,4-thiadiazol-2-ylthio): IR ($CHCl_3$) 1790, 1730, and 1698 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.30 (3H, s), 2.78 (3H, s), 4.58 (2H, s), 5.34 (1H, d, J=4.4 Hz), 5.35 (2H, s), 5.81 (1H, s), 6.05 (1H, dd, J=4.4 and 9.6 Hz), and 6.7—7.6 (11H, m).

Found: C, 55.11; H, 4.38%. Calcd for $C_{26}H_{24}N_4O_5S_3$: C, 54.91; H, 4.25%.

Compound **4j** (Nu=allyloxy): IR ($CHCl_3$) 1782, 1722, and 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.15 (3H, s), 4.15 (2H, m), 4.54 (2H, s), 4.92 (1H, s), 5.10 (1H, d, J=4.4 Hz), 5.28 (2H, s), 5.0—5.5 (3H, m), 5.94 (1H, dd, J=4.4 and 8.8 Hz), and 6.8—7.5 (11H, m).

Found: C, 63.23; H, 5.28%. Calcd for $C_{26}H_{26}N_2O_6S$: C, 63.14; H, 5.30%.

References

1) a) S. Torii, H. Tanaka, M. Sasaoka, N. Saitoh, T. Siroi, and J. Nokami, *J. Bull. Soc. Berg.*, **91**, 951 (1982); b) "Topics in Antibiotic Chemistry," ed by E. D. Sammes, Ellis Horwood Limited, Chichester (1980), Vol. 4; c) "Recent Advances in the Chemistry of β-Lactam Antibiotics," ed by G. I. Gregory, The Royal Society of Chemistry, Burlington House, London (1980).

2) For the review see, Ref. 1b, p. 173.

3) a) T. Kamiya, T. Teraji, M. Hashimoto, O. Nakaguchi, and T. Oku, *J. Am. Chem. Soc.*, **98**, 2342 (1976); b) D. O. Spry, *Tetrahedron Lett.*, **1977**, 3611; c) D. H. Bremner and M. M. Campbell, *J. Chem. Soc., Perkin Trans. 1*, **1977**, 2298.

4) D. O. Spry, *Tetrahedron Lett.*, **21**, 1289 (1980).

5) a) W. H. Koster, J. E. Dolfini, and B. Toeplity, *J. Org. Chem.*, **43**, 79 (1978); b) G. Franceschi, M. Foglio, P. Masi, A. Surato, G. Palamidessi, L. Bernardi, F. Arcamone, and G. Cainelli, *J. Am. Chem. Soc.*, **99**, 248 (1977); c) D. O. Spry, *Tetrahedron Lett.*, **1972**, 3717.

6) C. U. Kim and D. N. McGregor, *Tetrahedron Lett.*, **1978**, 409; see also Refs. 2 and 5.

7) a) H. E. Applegate, C. M. Cimarusti, J. E. Dolfini, P. T. Funke, W. H. Koster, M. S. Puar, W. A. Slusarchyk, and M. G. Young, *J. Org. Chem.*, **44**, 811 (1979); b) W. A. Slusarchyk, H. E. Appligate, C. M. Cimarusti, J. E. Dolfini, P. Funke, and M. Puar, *J. Am. Chem. Soc.*, **100**, 1886 (1978); see also Ref. 5a.