SYNTHESIS AND BIOLOGICAL ACTIVITIES OF C-3 HETEROCYCLYL CARBON-SUBSTITUTED NEW CEPHALOSPORINS

HOKOON PARK*, JAE YEOL LEE, YONG SUP LEE, JONG OK PARK, SUNG BO KOH and WON-HOON HAM

Organic Chemistry Laboratory (I), Korea Institute of Science and Technology, P. O. Box 131, Cheongryang, Seoul 130-650, Korea

(Received for publication December 14, 1993)

Chemical manipulation of the C-3 position in the cephalosporin molecule has resulted in the discovery of numerous novel antibiotics. In general, the C-3 position of the cephalosporins was substituted with heterocyclyl sulfurs or nitrogens.[1~3] In the course of our research on the modification of cephalosporin at the C-3 position, our efforts have been focused on synthesizing new cephalosporins substituted with heterocyclyl carbon at the C-3 position. Although recent papers concerning the coupling reaction of chloromethylcephem with vinylstannanes have appeared,[4,5] there is no report for the coupling reaction of chloromethylcephem with heterocyclylstannanes. Thus, we are interested in displacement at the C-3 position by heterocyclic carbon nucleophiles to afford a new type of cephalosporins. Here we wish to report the synthesis and the antimicrobial activities of 3-heterocyclyl carbon-substituted cephalosporins.

Most of the new cephalosporins were synthesized according to the general procedure shown in Scheme 1.

The C-C bond formation was accomplished by the reaction of chloromethylcephem **1** with a variety of heterocyclylstannanes (**2a~2i**) by the previously known method[4,5] as shown in Table 1. The reaction is illustrated by the preparation of the thiophene compound, **3a**.

Reaction of 3-chloromethylcephem **1** with 1.05 equiv of 2-tributylstannanylthiophene (**2a**) in the presence of bis(dibenzylideneacetonyl)palladium ($Pd(dba)_2$, 2 mol%) and tri(2-furyl)phosphine (4 mol%) in refluxing THF afforded 3-(2-thienyl)-methylcephem (**3a**) in 87% yield: NMR (60 MHz, $CDCl_3$) δ 3.30 (2H, br s, 2-H), 3.63 (2H, s, $PhCH_2$), 3.95 (2H, br s, 3'-H), 5.02 (1H, d, J=5 Hz, 6-H), 5.88 (1H, dd, J=5, 10 Hz, 7-H), 6.4~7.1 (4H, m, thienyl and NH), 7.43 (16H, m, 3Ph and diphenyl-CH). The reaction of 3-chloromethylcephem **1** with other heterocyclylstannanes (**2b~2i**) also proceeded smoothly in 30~92% yield (Table 1).

2-Tributylstannanylthiophene (**2a**) was prepared in 95% yield by the treatment of thiophene with

Scheme 1.

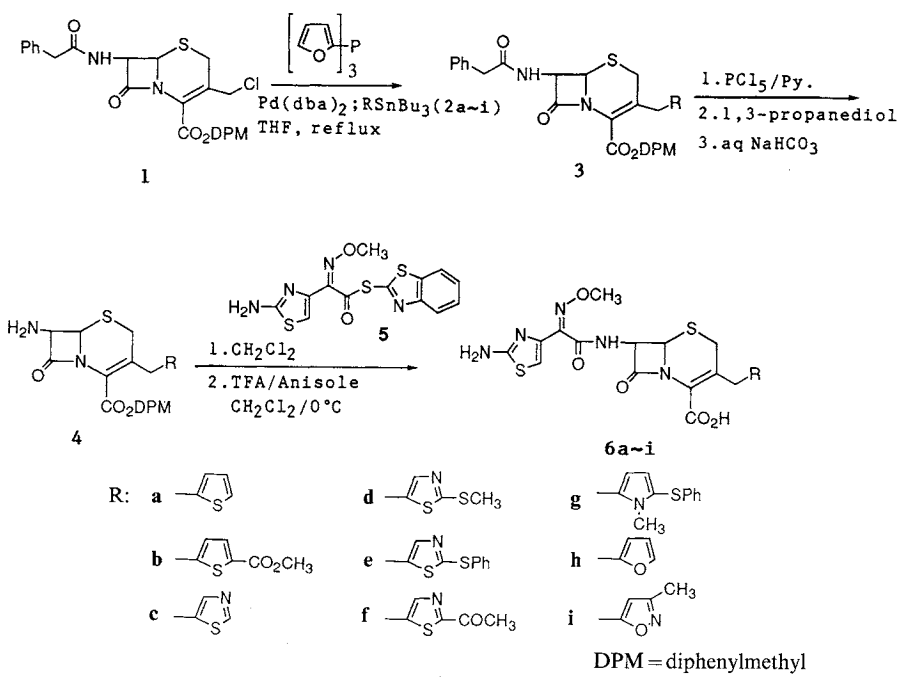
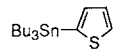
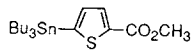
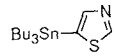
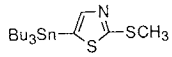
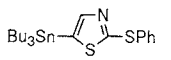
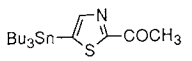
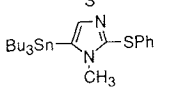
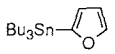
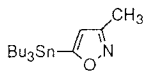


Table 1. Coupling of heterocyclylstannanes (**2a**~**2i**) with 3-chloromethylcephem **1**.

Compound	Stannane (%)[a]		Reaction time (hours)	Yield(%)
3a		**2a** (95)	2.5	87
3b		**2b** (57)	5	75
3c		**2c** (84)[b]	24	30
3d		**2d** (62)	10	75
3e		**2e** (92)	5	70
3f		**2f** (57)	19	61
3g		**2g** (87)	5	62
3h		**2h** (88)	1	92
3i		**2i** (80)	14	56

[a] Yields in parenthesis are the isolation yields of the heterocyclylstannanes from the corresponding heterocycles.
[b] **2c** was prepared from 2-(trimethylsilyl)thiazole.

Table 2. *In vitro* antimicrobial activity of cephalosporins (MIC μg/ml).

Compound	*S.p.*	*S.a.*	*E.c.*	*P.a.*	*K.a.*	*En.c.*
6a	<0.002	1.56	0.1	>100	0.78	>100
6b	<0.002	0.78	0.05	>100	1.56	>100
6c	<0.002	0.78	0.05	>100	0.2	>100
6d	0.05	6.25	0.39	25	0.78	>100
6e	<0.002	0.78	0.05	>100	3.13	>100
6f	0.007	1.56	0.03	>100	0.78	>100
6g	<0.002	1.56	0.03	>100	12.5	>100
6h	0.78	25	1.56	>100	0.39	>100
6i	0.01	3.13	0.1	>100	0.39	>100
Cefixime	0.1	25	0.1	100	0.05	>100
Cefotaxime	0.007	1.56	0.007	12.5	0.01	>100

Abbreviations: *S.p.*, *Streptococcus pyogenes* 308A; *S.a.*, *Staphylococcus aureus* SG511; *E.c.*, *Escherichia coli* DC2; *P.a.*, *Pseudomonas aeruginosa* ATCC 9027; *K.a.*, *Klebsiella aerogenes* 1522E; *En.c.*, *Enterobacter cloacae* 1321E.

n-butyllithium (1 equiv) and tributyltin chloride (1 equiv) at 0°C in ether solution: NMR (60 MHz, $CDCl_3$) δ 0.8~1.8 (27H, m, 3Bu), 6.67 (1H, dd, J=1, 2 Hz), 6.75 (1H, d, J=2 Hz), 7.90 (1H, d, J=1 Hz). The other heterocyclylstannanes were obtained in a similar manner from the corresponding heterocycles except for **2b** and **2f**, which used lithium diisopropylamide as the base. Heterocyclystannane **2b** was prepared by the reaction of thiophene 2-carboxylic acid with lithium diisopropylamide (2.2 equiv) and tributyltin chloride (1 equiv, −78°C to 25°C, 20 hours) and acidic workup followed by the treatment of excess diazomethane (at 0°C) in THF. Removal of the phenylacetyl group of **3** using phosphorous pentachloride - 1,3-propanediol[6] - $NaHCO_3$ and acylation of the resulting free amines **4** with aminothiazole active ester **5**[7] and finally, removal of the diphenylmethyl group with trifluoroacetic acid provided the corresponding 3-heterocyclyl carbon-substituted cephalosporins (**6a**~**6i**) as trifluoroacetic acid salts. **6a**: NMR (200 MHz, DMSO-d_6) δ 3.40 and 3.68 (2H, ABq, J=17.9 Hz,

2-H), 3.95 (3H, s, OCH_3), 3.87 and 4.17 (2H, ABq, $J=14.7$ Hz, 3'-H), 5.26 (1H, d, $J=4.6$ Hz, 6-H), 5.82 (1H, dd, $J=4.6$, 8.0 Hz, 7-H), 6.90 (1H, s, aminothiazole-H), 7.03 (2H, m, thienyl), 7.46 (1H, m, thienyl), 9.76 (1H, d, $J=8$ Hz, amide NH).

The MICs of the new cephalosporins (**6a**~**6i**) against selected Gram-positive and Gram-negative bacteria were determined by an *in vitro* agar dilution technique (Table 2). For comparison, the MIC values of cefixime and cefotaxime are listed.

Most of the compounds were superior to cefixime and comparable to cefotaxime in microbial activity against *Streptococcus pyogenes* 308A and *Staphylococcus aureus* SG511, and comparable to cefixime against *Escherichia coli* DC2. In this series, thiophene and thiazole derivatives **6b**~**6f** exhibited especially good activities. However, they were less active than cefixime against *Klebsiella aerogenes* 1522E and essentially inactive (with the notable exception of **6d**) against *Pseudomonas aeruginosa* ATCC 9027 and *Enterobacter cloacae* 1321E.

The 3-heterocyclyl carbon-substituted cephalosporins showed as good antibacterial activities as cefotaxime against Gram-positive bacteria. However further studies in evaluating activities against Gram-negative organism will be necessary.

Acknowledgments

The financial support by the Ministry of Science and Technology, Korea is gratefully acknowledged.

References

1) NAKAYAMA, E.; K. WATANABE, M. MIYAUCHI, K. FUJIMOTO & J. IDE: Studies on orally active cephalosporin esters. VI. Synthesis and antimicrobial activity of 3-(3-isoxazolyl)oxymethylcephalosporin derivatives. J. Antibiotics 43: 1122~1130, 1990
2) NAKANISHI, E.; Y. OGASAWARA, Y. SASAKI & N. YASUDA: Synthesis and structure-activity relationships of 3-(2-imidazolyl)thiomethyl cephalosporins. J. Antibiotics 42: 54~62, 1989
3) BLUMBACH, J.; W. DÜRCKHEIMER, E. EHLERS, K. FLEISCHMANN, N. KLESEL, M. LIMBERT, B. MENCKE, J. REDEN, K. H. SCHEUNEMANN, E. SCHRINNER, G. SEIBERT, M. WIEDUWILT & M. WORM: Cefodizime, an aminothiazolylcephalosporin. V. Synthesis and structure-activity relationships in the cefodizime series: J. Antibiotics 40: 29~42, 1987
4) FARINA, V.; S. R. BAKER, D. A. BENIGNI, S. I. HAUCK & C. SAPINO, JR.: Palladium catalysis in cephalosporin chemistry: General methodology for the synthesis of cephem side chains. J. Org. Chem. 55. 5833~5847, 1990
5) FARINA, V.; S. R. BAKER, D. A. BENIGNI & C. SAPINO, JR.: Palladium-catalyzed coupling between cephalosporin derivatives and unsaturated stannanes: A new ligand for palladium chemistry: Tetrahedron Lett. 29: 5739~5742, 1988
6) ABURAKI, S.; H. KAMCHI, Y. NARITA, J. OKAMURA & T. NAITO (Bristol-Myers): Cephalosporins. U. S. Pat. 4,406,899, Sep. 27, 1983
7) PRAGER, B.: Preparation of a crystalline cephalosporin. (Biochemie G.m.b.H.) Austrian 387,022, Nov. 25, 1988