Synthesis and Biological Activity of C-3 Direct Heterocyclylcarbon-substituted Novel Cephalosporins

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Chemical modification of the C-3 position of cephalosphorins has resulted in the discovery of numerous novel antibiotics. Recently, considerable interest has been focused on the direct heteroatom substitution[1,2] or direct olefinic carbon substitution at the C-3 position[3,4] of the cephem nucleus.

In our previous paper, we have reported the synthesis and biological activities of the C-3′ heterocyclylcarbon-substituted cephalosporin derivatives[5]. In continuation with our research on β-lactam antibiotics by the introduction of heterocycles at the C-3 position, we were interested in direct substitution of heterocyclylcarbon at the C-3 position based on Farina's chemistry[1,6]. Although several cephalosporin derivatives containing an olefinic side chain at the C-3 position such as cefixime and cefzil have been prepared, examples of direct heterocyclylcarbon-substituted cephalosporin derivatives were rare.[1] In this paper, we report the synthesis and antimicrobial activity of direct heterocyclylcarbon-substituted cephalosporins at the C-3 position. The substituent effect at oxyimino group in the acyl side chain of new cephalosporins was also examined.

The necessary heterocycles (**2a**~**2d**) were prepared according to a reported procedure[5]. Most of the new cephalosporins were synthesized according to the general procedure as shown in Scheme 1.

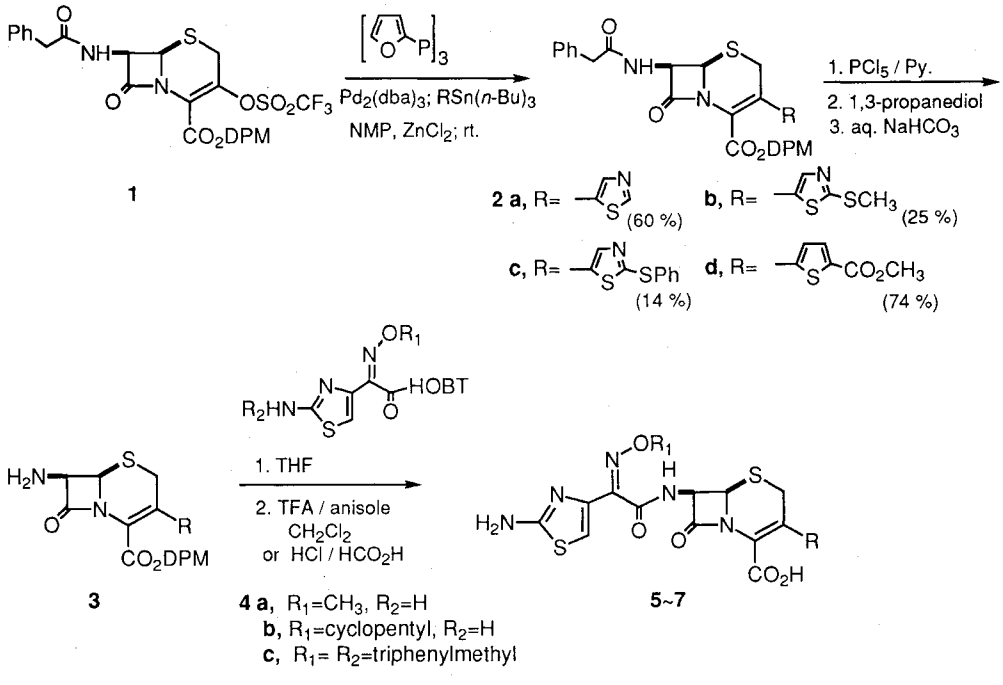
The C-C bond formation by the direct substitution of heterocycles was accomplished by the reaction of vinyl triflate **1** with a variety of heterocyclylstannanes (**2a**~**2d**). The reaction is illustrated by the preparation of the thiazole compound, **2a**.

Reaction of vinyl triflate **1** with 1.1 equiv. of 5-thiazolyl-tri-*n*-butylstannane in the presence of 2 equiv. of $ZnCl_2$, tri(2-furyl)phosphine (4 mol%), and Pd_2dba_3 (2 mol%) in N-methylpyrrolidone (NMP) at room temperature afforded 3-(5-thiazolyl)cephem (**2a**) in 60% yield: NMR (300 MHz, $CDCl_3$) δ 3.45~3.74 (4H, m, 2-H and CH_2Ph), 5.06 (1H, d, J=4.5 Hz, 6-H), 5.93 (1H, dd, J=4.5, 8.9 Hz, 7-H), 6.16 (1H, d, J=8.9 Hz, amide), 6.88 (1H, s, $CHPh_2$), 7.04~7.40 (15H, m, Ph), 7.55 (1H, s, thiazole-H), 8.62 (1H, s, thiazole-H). The reaction of vinyl triflate **1** with other heterocyclylstannanes also proceeded in 14~74% yield as shown in Scheme 1.

The phenylacetyl group side chain of **2a** was cleaved by the standard method (PCl_5-1,3-propanediol-$NaHCO_3$) to give 7-amino cephalosporin derivative (**3a**) in 91% yield.

In order to examine the substituent effect at oxyimino

Scheme 1. Synthesis of C-3 heterocyclylcarbon-substituted cephalosporins.



NMP = N-methylpyrrolidone, DPM = diphenylmethyl, HOBT = hydroxybenzotriazole

Table 1. Yield, IR and ^{1}H NMR data of cephalosporin derivatives (**5**~**7**).

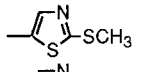
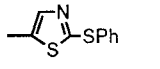
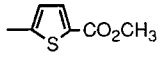
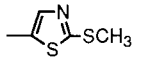
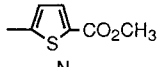
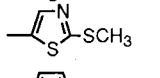
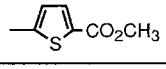
com-pound	R	R_1	Yield from **3** (%)	IR (KBr, cm^{-1})	^{1}H NMR (300 MHz, δ in CD_3OD, ppm)			
					Thiazole-H	6-H, 7-H (d, J = 4 ~ 5 Hz)		OCH_3
5a		CH_3	81	1774	6.97	5.94	5.29	4.03
5b		CH_3	71	1774	7.07	5.92	5.27	4.06
5c		CH_3	38	1774	6.83	5.86	5.19	3.97
5d		CH_3	64	1774	7.03	5.96	5.30	4.06 3.87
6a			61	1774	6.94	5.96	5.31	-
6b			78	1772	7.00	5.90	5.23	-
6c			68	1774	7.03	5.97	5.29	3.84
7a		H	17	1780	7.10	5.99	5.34	-
7b		H	13	1774	7.10	5.95	5.29	-
7c		H	12	1776	7.38	5.96	5.29	3.84

Table 2. *In vitro* antimicrobial activity of cephalosporins (**5**~**7**).

Test organism	MIC (μg/ml)											
	5a	**5b**	**5c**	**5d**	**6a**	**6b**	**6c**	**7a**	**7b**	**7c**	**CFX**	**CTX**
S. pyogenes A 308	0.007	0.004	0.007	0.013	0.013	0.007	0.007	0.007	0.004	0.013	0.098	0.007
S. pyogenes A 77	0.007	0.007	0.004	0.007	0.013	0.007	0.007	0.007	0.004	0.007	0.049	0.007
S. faecium MD 8b	100	50	25	25	50	25	12.5	25	12.5	12.5	>100	100
S. aureus SG 511	3.13	1.56	6.25	3.13	1.56	1.56	1.56	0.39	0.78	0.78	50	1.56
S. aureus 285	6.25	3.13	12.5	6.25	3.13	1.56	1.56	0.78	1.56	1.56	50	1.56
S. aureus 503	1.56	1.56	3.13	1.56	0.78	0.78	0.78	0.2	0.39	0.2	50	0.78
E. coli O 55	0.98	0.98	0.39	0.98	1.56	1.56	0.78	0.2	0.98	0.98	0.2	0.013
E. coli DC 0	0.2	0.39	0.78	0.39	3.13	1.56	1.56	0.39	0.39	0.39	0.78	0.025
E. coli DC 2	0.098	0.013	0.098	0.013	0.39	0.049	0.098	0.39	0.098	0.049	0.39	0.013
E. coli TEM	0.39	0.39	1.56	0.39	3.13	1.56	1.56	0.78	0.78	0.39	0.78	0.025
E. coli 1507 E	0.2	0.2	0.2	0.39	6.25	3.13	1.56	0.2	0.39	0.2	0.39	0.025
P. aeruginosa 9027	>100	>100	>100	>100	>100	100	100	>100	>100	>100	>100	25
P. aeruginosa 1592 E	>100	>100	>100	>100	>100	100	100	>100	>100	>100	>100	12.5
P. aeruginosa 1771	100	50	100	50	>100	100	100	>100	>100	50	12.5	6.25
P. aeruginosa 1771 M	0.78	0.78	6.25	1.56	0.39	0.39	0.39	3.13	6.25	3.13	0.2	0.049
S. typhimurium	0.098	0.098	0.78	0.2	3.13	0.78	1.56	0.098	0.2	0.098	0.098	0.025
K. oxytoca 1082 E	3.13	3.13	50	3.13	6.25	6.25	6.25	25	100	12.5	0.39	0.78
K. aerogenes 1522 E	0.049	0.098	1.56	0.2	3.13	3.13	3.13	0.098	0.2	0.098	0.025	0.025
E.cloacae P 99	>100	>100	>100	>100	>100	100	100	>100	>100	>100	>100	25
E.cloacae 1321 E	0.098	0.2	0.78	0.2	1.56	1.56	0.78	0.098	0.2	0.098	0.013	0.007

Abbreviations: CFX; cefixime, CTX; cefotaxime.

group in the acyl side chain of the C-7 position, the coupling reaction was carried out with several aminothiazole active esters (**4a**~**4c**) (Table 1).

Reaction of **3a** with 1.1 equiv. of hydroxybenzotriazole active ester (**4a** or **4b**) in THF followed by removal of diphenylmethyl group with trifluoroacetic acid and anisole provided new 3-thiazolyl carbon-substituted cephalosporin derivatives (**5a** or **6a**) in 81% and 61% yield, respectively. **5a**: IR (KBr): 3366, 1774, 1676 cm^{-1}; ^{1}H NMR (CD_3OD) δ 3.74 and 3.88 (2H, ABq, J= 18.3 Hz, 2-H), 4.03 (3H, s), 5.29 (1H, d, J=4.8 Hz, 6-H), 5.94 (1H, d, J=4.8 Hz, 7-H), 6.97 (1H, s, aminothiazole-

H), 7.84 (1H, s, thiazole-H), 9.01 (1H, s, thiazole-H).

C-7 hydroxyimino derivatives (**7a**~**7c**) were obtained by the reaction with N- and O-trityl protected aminothiazole active ester (**4c**). The trityl and diphenylmethyl protecting groups were removed with formic acid and HCl to afford the desired compounds (**7a**~**7c**).

The MICs of new cephalosporins against Gram-positive and Gram-negative bacteria were determined by an *in vitro* agar dilution method (Table 2). For comparison, the MIC data of cefixime and cefotaxime are listed.

The effects of various substituents at oxyimino group in the acyl side chain of the C-7 position and the C-3 heterocyclic substituents were examined. Most of the compounds were superior to cefixime against Gram-positive organism. However, they were less active than cefixime and cefotaxime against *Klebsiella oxytoca*, and nearly inactive against *Pseudomonas aeruginosa* and *Enterobacter cloacae*. C-7 hydroxyimino or cyclopentyloxyimino derivatives (**6a**~**7c**) exhibited higher level of activity than that of C-7 methoxyimino derivatives (**5a**~**5d**) against *Staphylococcus aureus*. Notably, most of the compounds exhibited some level of activity against *Streptococcus faecium* MD 8b, which is resistant to cefixime and cefotaxime.

These results demonstrate direct C-3 heterocyclyl-carbon-substituted cephalosporins (**5**~**7**), having methoxyimino-, cyclopentyloxyimino- or hydroxyimino-thiazole moiety at the C-7 position are more active than cefixime and comparable to cefotaxime in antibacterial activity against Gram-positive bacteria, but are less active against *Klebsiella oxytoca*.

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