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A NEW SYNTHETIC ROUTE TO 7α-METHOXYCEPHALOSPORINS

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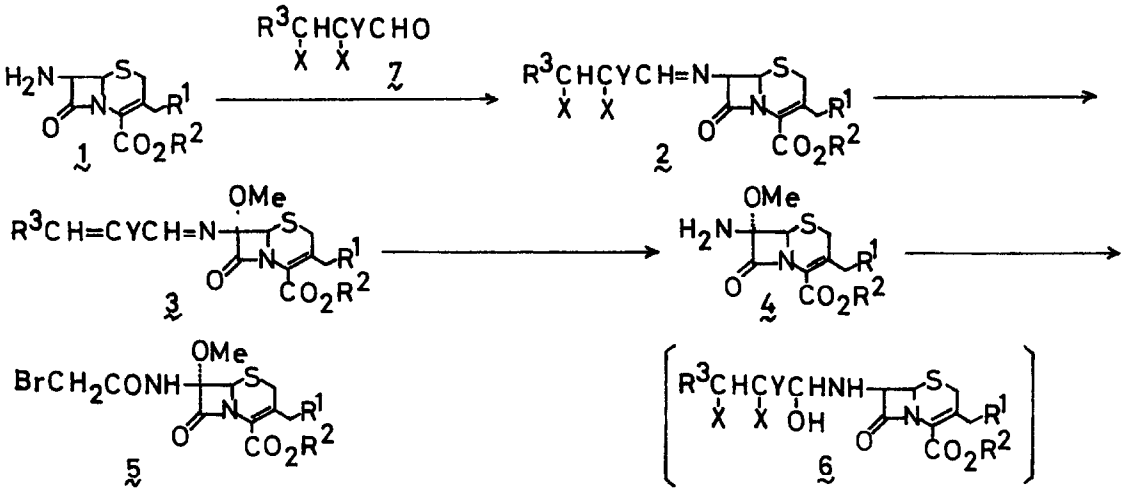
Summary: Treatment of 7β-(2,2,3-trihaloalkylideneamino)cephalosporins with excess methanol in the presence of acid scavenger gave 7β-(2-haloalk-2-enylideneamino)-7α-methoxycephalosporins.

Since isolation of cephamycins (7α-methoxycephalosporins) from cultures of streptmyces species and subsequent modification of the original compound to those with enhanced activity,[1] many attempts have been made to introduce a methoxy group at the seven position of the cephalosporin nucleus.[2] However, some difficulty still remains either in the synthesis of 7α-methoxycephalosporins having a complex 7β-acylamino side chain or in the large scale preparation (especially, in the industrial production) of these compounds.

We now wish to report a new method for the preparation of 7β-acylamino-7α-methoxycephalosporins 5 from 7β-aminocephalosporins 1 via 7β-amino-7α-methoxycephalosporins 4. This method involves a one-pot conversion of 7β-(2,2,3-trihaloalkylideneamino)cephalosporins 2 into 7β-(2-haloalk-2-enylideneamino)-7α-methoxycephalosporins 3. In this procedure, any oxidizing agents are not needed and a strong base as lithium methoxide is not necessary either. Thus 7β-aminocephalosporins 1 were converted into 7β-acylamino-7α-methoxycephalosporins 5 in high yields under extremely mild conditions.



The Schiff bases 2 were prepared in good yields from the aducts 6, which were formed by treating the amino esters 1 with a stoichiometric amount of trihaloaldehydes 7,[3] by the reaction with thionyl chloride in the presence of N,N-dimethylaniline. In the case of X=Y=Cl, the Schiff bases 2 were also prepared in high yields from 1 and 7 (or the hydrates of 7) by a usual azeotropic distillation method. These results are summerized in Table 1.

Table 1. Preparation of the Schiff bases 2[4]

1		7					
R^1	R^2	R^3	X	Y	Method[a)]	Solvent	Yield of 2 (%)
H	t-Bu	CH_3	Cl	Cl	A	CH_2Cl_2	quant.
OAc	t-Bu	CH_3	Br	Cl	A	CH_2Cl_2	95
STz[b)]	$CHPh_2$	H	Br	Br	A	CH_2Cl_2	71
STz[b)]	$CHPh_2$	CH_3	Br	Cl	A	CH_2Cl_2	70
STz[b)]	$CHPh_2$	Ph	Br	Br	A	CH_2Cl_2	33
STz[b)]	$CHPh_2$	CH_3	Cl	Cl	B	CH_2Cl_2	85
STz[b)]	$CHPh_2$	CH_3	Cl	Cl[c)]	B	CH_2Cl_2	94
STz[b)]	$CHPh_2$	Ph	Cl	Cl	B	CH_2Cl_2	84
STz[b)]	$CHPh_2$	Ph	Cl	Cl[c)]	B	1)CH_2Cl_2,2)AcOEt	95

a) Method A: After the solution of 1 and 7 had been stirred for 0.5hr. at 0 °C, the mixture was treated by 1.5eq. of $SOCl_2$ in the presence of 5eq. of $PhNMe_2$ for 1hr. at -20 °C.
Method B: The azeotropic distillation method by use of the solvent or the solvents.
b) Tz=1-methyl-1H-tetrazol-5-yl.
c) The hydrate of 7 was used.

Treatment of the Schiff bases 2 with excess methanol in the presence of acid scavenger such as borax ($Na_2B_4O_7 10H_2O$) or lithium methoxide afforded 7α-methoxy derivatives 3 in good yields. (See Table 2.) The mechanism of this reaction should be the formation of an imine derivative 8 from 2 through the 1,4-elimination with the acid scavenger followed by the 1,5-substitution of the 3'-halogen (on 8) for the 7α-methoxy group (on 3).[5]

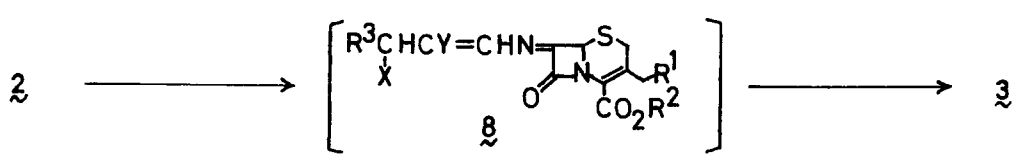


Table 2. Conversion of the Schiff bases 2 into the 7α-methoxy derivatives 3[6,7]

2								
R^1	R^2	R^3	X	Y	Acid scavenger	Temp.(°C)	Solvent	Yield of 2 (%)[a]
H	t-Bu	CH_3	Cl	Cl	CH_3OLi[b]	-50[d]	THF	71
OAc	t-Bu	CH_3	Br	Cl	Borax[b]	0[e]	CH_2Cl_2	68
STz	$CHPh_2$	H	Br	Br	CH_3OLi[b]	-78[d]	THF	51
STz	$CHPh_2$	CH_3	Br	Cl	Borax[b]	0[e]	CH_3CN	75
STz	$CHPh_2$	Ph	Br	Br	Borax[b]	room temp.[f]	CH_2Cl_2	71
STz	$CHPh_2$	Ph	Cl	Cl	Borax[b]	0[e]	CH_3CN	87
STz	$CHPh_2$	Ph	Cl	Cl	Borax[c]	0[e]	AcOEt	86

a) Isolated yields by preparative TLC or flash column chromatography. b) 3Eq. of CH_3OLi or borax was used. c) 2.5Eq. of borax was used. d) The reaction was carried out for 15min. under argon. e) The reaction was carried out for 2 or 3hr. f) The reaction was carried out for 0.5hr.

Removal of the 7β-N-alkenylidene moiety of 3 with Girard reagent T ((carboxymethyl)trimethylammonium chloride hydrazide) in the presence of acetic acid or p-toluenesulfonic acid followed by quenching with aqueous solution of sodium hydrogen carbonate gave free amines 4. Without purification, the amines 4 were converted into bromoacetoamides 5 in good yields by a usual acylation method. (See Table 3.) The resulting amide 5 (R^1=1-methyl-1H-tetrazol-5-ylthio) is a key intermediate for synthesizing some of the useful cephamycin-group antibiotics (e.g. cefmetazole,[8] MT-141[9]).

Table 3. Synthesis of the bromoacetoamides 5[10,11]

3				Condition of the 1st. process[a),b)]			Yield of 5[c)]
R^1	R^2	R^3	Y	Acid	Temp.(°C)	Period(hr.)	from 3 (%)
OAc	t-Bu	CH_3	Cl	AcOH[d]	room temp.	2	50
STz	$CHPh_2$	CH_3	Cl	AcOH[d]	0	4.5	64
STz	$CHPh_2$	Ph	Cl	AcOH[d]	0	4	68
STz	$CHPh_2$	Ph	Cl	p-TsOH[e]	-20	2	72
STz	$CHPh_2$	Ph	Cl	p-TsOH[f]	-40	1	90

a) A mixture of ethyl acetate and methanol was used as the solvent. b) The 2nd. process: Acylation with $BrCH_2COBr$ in the presence of $PhNMe_2$ in ethyl acetate at -20°C. c) Isolated yields by preparative TLC or flash column chromatography. d) 5Eq. of Girard T and 10eq. of AcOH were used. e) 3Eq. of Girard T and 0.2eq. of p-TsOH were used. f) 2Eq. of Girard T and 2eq. of p-TsOH were used.

References and Notes

1. a) H. Nakao, H. Yanagisawa, B. Shimizu, M. Kaneko, M. Nagano, and S. Sugawara, J. Antibiot., 29, 554 (1976) and references cited therein; b) R. M. DeMarinis, J. V. Uri, and J. A. Weisbach, J. Antibiot., 29,973 (1976); c) H. E. Applegate, C. M. Cimarusti, J. E. Dolfini, W. H. Koster, M. A. Slusarchyk, and M. G. Young, ibid., 31, 561 (1978).
2. a) E. M. Gordon, H. W. Chang, and C. M. Cimarusti, J. Am. Chem. Soc., 99, 5504 (1977) and references cited therein; b) T. Kobayashi and T. Hiraoka, Chem. Pharm. Bull. (Tokyo), 27, 2718 (1979); c) T. Kobayashi and T. Hiraoka, Bull. Chem. Soc. Jpn., 52, 3366 (1979).
3. Preparation of 2,2,3-trichlorobutanal: Organic Syntheses, coll. vol. IV, 130 (1962), the other aldehydes were synthesized similarly from the corresponding α,β-unsaturated aldehydes or α-halo-α,β-unsaturated aldehydes.
4. All of these compounds were confirmed by IR and NMR; typical spectral data are shown below. 2(R^1=STz, R^2=CHPh$_2$, R^3=Ph, X=Y=Cl); NMR($CDCl_3$): δ=3.67(2H, broad s), 3.80(3H, s), 4.20(1H, d, J=14Hz), 4.42(1H, d, J=14Hz), 5.12(1H, d, J=5Hz), 5.37-5.51(1H, m), 5.54(1H, broad s), 6.92(1H, s), 7.1-7.7(15H, m), 8.20+8.28(1H, d+d, J=2Hz), IR(KBr disk): ν=1780, 1720cm^{-1}.
5. It was reported that similar imine derivatives (7-(1-chloroalk-1-enylimino)-cephalosporins) were produced from α-haloimino chlorides (7β-(1-chloro-2-haloalkylideneamino)cephalosporins) via 1,4-elimination with CH_3OLi: Y. Sugimura, K. Iino, Y. Iwano, T. Saito, and T. Hiraoka, Tetrahedron Lett.,1307 (1976).
6. All of these compounds were confirmed by IR and NMR; typical spectral data are shown below. 3(R^1=STz, R^2=CHPh$_2$, R^3=Ph, Y=Cl); NMR($CDCl_3$): δ=3.59(3H, s), 3.64(2H, broad s), 3.81(3H, s), 4.24(1H, d, J=14Hz), 4.43(1H, d, J=14Hz), 5.09(1H, s), 6.92(1H, s), 7.1-7.7(14Hz, m), 7.7-7.9(2H, m), 8.33(1H, s), IR(KBr disk): ν=1778, 1720, 1605(1610shoulder)cm^{-1}.
7. 7β-Methoxy isomers were not detected.
8. 7β-(((Cyanomethyl)thio)acetamido)-7α-methoxy-3-(((1-methyl-1H-tetrazol-5-yl)-thio)methyl)-3-cephem-4-carboxylic acid: See ref. 1a).
9. 7β-(((2(R)-2-Amino-2-carboxyethyl)thio)acetamido)-7α-methoxy-3-(((1-methyl-1H-tetrazol-5-yl)thio)methyl)-3-cephem-4-carboxylic acid: T. Watanabe, K. Kawarajo, T. Tsuruoka, Y. Kazuno, and T. Niida, the 20th. Interscience Conference on Antimicrobial Agents and Chmotherapy, New Orleans, U.S.A., Sept. 1980, Abstracts 161.
10. All of these compounds showed IR and NMR spectra identical with those of the authentic samples prepared by known methods.[2]
11. The epimerization on the 7-carbon atom was not observed.

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