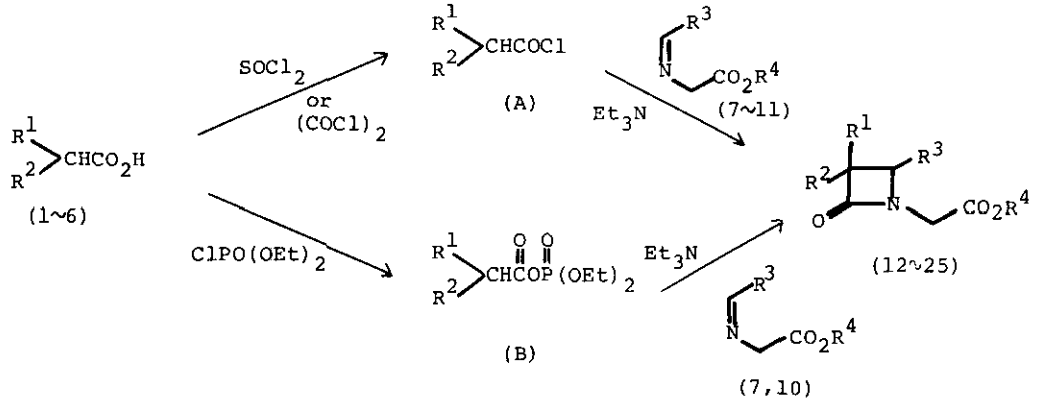
STUDIES ON THE SYNTHESIS OF HETEROCYCLIC COMPOUNDS 775. SYNTHESIS OF β-LACTAMS BY ACID CHLORIDE- AND PHOSPHATE ANHYDRIDE-IMINE METHODS

Tetsuji Kametani*, Shuichi Yokohama, Yuichi Shiratori, Sinko Aihara, and Keiichiro Fukumoto
Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan
Fumio Satoh
The Sendai Institute of Heterocyclic Chemistry, No. 53, Kawauchi-30-nincho, Sendai 980, Japan

Abstract — Several 1,3,4-substituted 2-azetidinones (12 ∿ 25) were synthesised by the acid chloride- and phosphate anhydride-imine methods.

There are various methods developed for the synthesis of β-lactams.[2,3] Among them, the acid chloride-imine method introduced by Bose and co-workers[4∿8] is one of the most general method for preparation of β-lactams. Recently they further found an alternative method using phosphorylating agents, in which the phosphate anhydride intermediate (B) was postulated.[9] We have synthesised several β-lactams by both methods and here wish to report these results.

Scheme 1



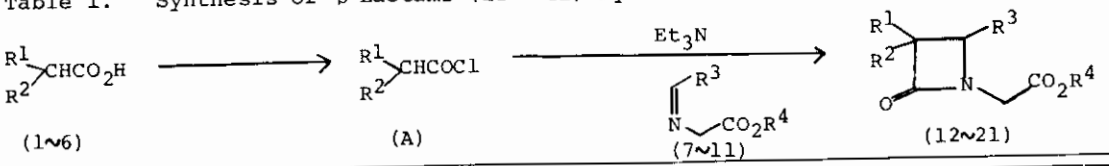
(A) Acid chloride-Imine Method

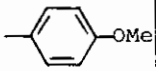
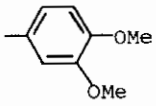
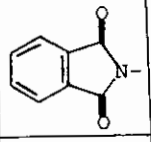
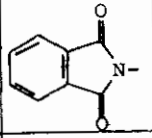
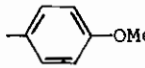
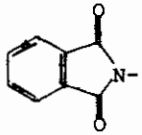
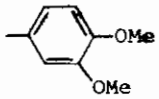
Commercially available carboxylic acids (1 ∿ 4) were firstly converted into the corresponding acid chlorides (A) with thionyl chloride or oxalyl chloride as usual. Diphenylacetyl chloride was treated with triethylamine according to Bachi's procedure[10] to give the ketene[11], which was added to a solution of N-benzylideneglycinates (7 ∿ 9) in dry benzene. The reaction was carried out overnight at room temperature. In the case of the other acid chlorides from the carboxylic acids (2 ∿ 4), the acid chlorides were directly added to a mixture of the imines (7 ∿ 11) and triethylamine in dry methylene chloride and the resulting mixture was stirred for 1 h at room temperature. The results are summarised in Tables 1 and 2.

(B) Phosphate Anhydride-Imine Method

After stirring an equimolecular mixture of the carboxylic acids (4 ∿ 6) and diethylphosphorochloridate in dry methylene chloride at room temperature for 20 min, the resulting solution was added dropwise to a stirred mixture of the imines (7,10) and triethylamine in dry methylene chloride and the resulting mixture was stirred overnight at the same temperature. The results are shown in Tables 3 and 4. It was varified from the nmr analysis based on the coupling constant due to the protons on the azetidinone ring that only trans-isomers (21 ∿ 25) were obtained by this method.

Table 1. Synthesis of β-Lactams (12 ∿ 21) by Acid chloride-Imine Method



Compound	R^1	R^2	R^3	R^4	yield (%)	mp (°C)	Formula	MS m/e (M^+)	Anal. Calcd. (Found) C	H	N
12	Ph	Ph	Ph	Et	79.0	100.5 ∿ 101	$C_{25}H_{23}NO_3$	385	77.90 (77.40)	6.01 (6.31)	3.63 (3.55)
13	Ph	Ph		Et	69.0	87 ∿ 88	$C_{26}H_{25}NO_4$	415	75.16 (75.16)	6.07 (6.11)	3.37 (3.34)
14	Ph	Ph		Et	66.0	130	$C_{27}H_{27}NO_5$	445	72.79 (72.72)	6.11 (6.32)	3.14 (3.02)
cis 15		H	Ph	Et	27.6	192 ∿ 193	$C_{21}H_{18}N_2O_5$	378	66.66 (66.38)	4.80 (4.75)	7.40 (7.36)
trans 15					15.0	oil	$C_{21}H_{18}N_2O_5$				
cis 16		H		Et	10.2	133	$C_{22}H_{20}N_2O_6$	408	64.70 (64.46)	4.94 (5.06)	6.86 (6.75)
trans 16					32.0	oil	$C_{22}H_{20}N_2O_6$	408	(64.51)	(5.24)	(6.89)
cis 17		H		Et	12.5	170 ∿ 171	$C_{23}H_{22}N_2O_7$	438	63.01 (63.00)	5.06 (5.17)	6.39 (6.49)
trans 17					43.7	oil	$C_{23}H_{22}N_2O_7 \cdot 0.25\ H_2O$	438	62.36 (62.47)	5.12 (5.44)	6.33 (6.07)

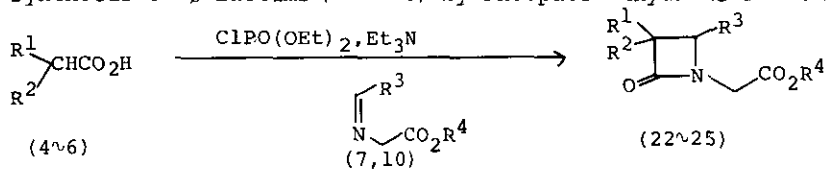
18	Cl	Cl	Ph	Et	26.8	oil	$C_{13}H_{13}NO_3Cl_2$	300,302, 304	
19	Cl	Cl		Et	8.0	oil	$C_{15}H_{15}NO_3Cl_2$	326,328, 330	
20	Cl	Cl		CH_2Ph	7.7	oil	$C_{20}H_{17}NO_3Cl_2$	289,301, 303	
21	SPh	H		CH_2Ph	30.0	oil	$C_{26}H_{23}NO_3S$	429	

Table 2 Spectral Data of the β-Lactams (12 ∿ 21)

Compound	IR($CHCl_3$) cm^{-1}	NMR (δ)
12	1760, 1740	(CCl_4): 1.20 (3H, t, J = 7 Hz, $CH_2\underline{CH_3}$), 3.45 (1H, d, J = 18 Hz, >C<$\frac{H}{H}$), 4.16 (2H, q, J = 7 Hz, $\underline{CH_2}CH_3$), 4.45 (1H, d, J = 18 Hz, >C<$\frac{H}{\underline{H}}$), 5.55 (1H, s, 4-H), 7.00 ∿ 7.66 (15H, m, 3 x Ph)
13	1760, 1740	(CCl_4): 1.20 (3H, t, J = 7 Hz, $CH_2\underline{CH_3}$), 3.36 (1H, d, J = 18 Hz, >C<$\frac{H}{H}$), 3.69 (3H, s, OMe), 4.15 (2H, q, J = 7 Hz, $\underline{CH_2}CH_3$), 4.40 (1H, d, J = 18 Hz, >C<$\frac{H}{\underline{H}}$), 5.46 (1H, s, 4-H), 6.60 (2H, d, J = 8 Hx, 2 x ArH), 6.83 ∿ 7.83 (12H, m, 12 x ArH)
14	1760, 1740	(CCl_4): 1.20 (3H, t, J = 7 Hz, $CH_2\underline{CH_3}$), 3.46 (1H, d, J = 18 Hz, >C<$\frac{H}{H}$), 3.48 (3H, s, OMe), 3.73 (3H, s, OMe), 4.13 (2H, q, J = 7 Hz, $\underline{CH_2}CH_3$), 4.32 (1H, d, J = 18 Hz, >C<$\frac{H}{\underline{H}}$), 5.40 (1H, s, 4-H), 6.26 (1H, s, ArH), 6.65 (2H, s, 2 x ArH), 7.03 ∿ 7.70 (10H, m, 2 x Ph)
cis 15	1770, 1740, 1720	($CDCl_3$): 1.33 (3H, t, J = 7 Hz, $OCH_2\underline{CH_3}$), 3.80 (1H, d, J = 18 Hz, >C<$\frac{H}{H}$), 4.26 (2H, q, J = 7 Hz, $O\underline{CH_2}CH_3$), 4.70 (1H, d, J = 18 Hz, >C<$\frac{H}{\underline{H}}$), 5.33 (1H, d, J = 5 Hz, 3 or 4-H), 5.66 (1H, d, J = 5 Hz, 3 or 4-H), 7.26 (5H, s, Ph), 7.63 (4H, s, 4 x ArH)
trans		($CDCl_3$): 1.33 (3H, t, J = 7 Hz, $OCH_2\underline{CH_3}$), 3.60 (1H, d, J = 18 Hz, >C<$\frac{H}{H}$), 4.03 (2H, q, J = 7 Hz, $O\underline{CH_2}CH_3$), 4.43 (1H, d, J = 18 Hz, >C<$\frac{H}{\underline{H}}$), 5.10 (1H, s, 3 or 4-H), 5.20 (1H, s, 3 or 4-H), 7.40 (5H, s, Ph), 7.76 (4H, s, 4 x ArH)
cis 16	1770, 1740, 1720	($CDCl_3$): 1.30 (3H, t, J = 7 Hz, $OCH_2\underline{CH_3}$), 3.66 (3H, s, OMe), 3.73 (1H, d, J = 18 Hz, >C<$\frac{H}{H}$), 4.26 (2H, q, J = 7 Hz, $O\underline{CH_2}CH_3$), 4.66 (1H, d, J = 18 Hz, >C<$\frac{H}{\underline{H}}$), 5.30 (1H, d, J = 5 Hz, 3 or 4-H), 7.20 (2H, d, J = 8 Hz, 2 x ArH), 7.63 (4H, s, 4 x ArH)
trans	1770, 1730, 1720	($CDCl_3$): 1.30 (3H, t, J = 7 Hz, $OCH_2\underline{CH_3}$), 3.53 (1H, d, J = 18 Hz, >C<$\frac{H}{H}$), 4.26 (2H, q, J = 7 Hz, $O\underline{CH_2}CH_3$), 4.66 (1H, d, J = 18 Hz, >C<$\frac{H}{\underline{H}}$), 5.26 (1H, S, 3 or 4-H), 5.33 (1H, s, 3 or 4-H), 6.96 (2H, J = 8 Hz, 2 x ArH), 7.33 (2H, d, J = 8 Hz, 2 x ArH), 7.56 ∿ 8.00 (4H, m, 4 x ArH)

cis 17	1775, 1740, 1730	($CDCl_3$): 1.35 (3H, t, J = 7 Hz, $OCH_2\underline{CH}_3$), 3.78 (3H, s, OMe), 3.83 (3H, s, OMe), 4.36 (2H, q, J = 7 Hz, $OC\underline{H}_2CH_3$), 4.70 (1H, d, J = 18 Hz, $>C<^{H}_{\underline{H}}$), 5.33 (1H, d, J = 6 Hz, 3 or 4-H), 5.69 (1H, d, J = 6 Hz, 3 or 4-H), 6.86 (3H, br s, 3 x ArH), 7.70 (4H, s, 4 x ArH),
trans	1775, 1730, 1720	($CDCl_3$): 1.30 (3H, t, J = 7 Hz, $OCH_2\underline{CH}_3$), 3.86 (3H, s, OMe), 3.90 (3H, s, OMe), 4.36 (2H, q, J = 7 Hz, $OC\underline{H}_2CH_3$), 4.66 (1H, d, J = 18 Hz, $>C<^{H}_{\underline{H}}$), 5.26 (1H, s, 3 or 4-H), 5.33 (1H, s, 3 or 4-H), 6.73 ∿ 7.06 (3H, m, 3 x ArH), 7.56 ∿ 7.99 (4H, m, 4 x ArH)
18	1790, 1740	(CCl_4): 1.25 (3H, t, J = 7 Hz, $OCH_2\underline{CH}_3$), 3.52 (1H, d, J = 18 Hz, $>C<^{H}_{\underline{H}}$), 4.18 (2H, q, J = 7 Hz, $OC\underline{H}_2CH_3$), 4.43 (1H, d, J = 18 Hc, $>C<^{H}_{\underline{H}}$), 5.33 (1H, s, 4-H), 7.23 ∿ 7.60 (5H, m, 5 x ArH)
19	1790, 1745	(CCl_4): 1.30 (3H, t, J = 7 Hz, $OCH_2\underline{CH}_3$), 3.67 (1H, d, J = 18 Hz, $>C<^{H}_{\underline{H}}$), 4.20 (2H, q, J = Hz, $OC\underline{H}_2CH_3$), 4.22 (1H, d, J = 18 Hz, $>C<^{H}_{\underline{H}}$), 4.82 (1H, d, J = 8 Hz, 4-H), 6.11 (1H, dd, J = 8 and 16 Hz, $\underline{H}>=<^{H}_{Ph}$), 6.83 (1H, d, J = 16 Hz, $H>=<^{H}_{Ph}$), 7.07 ∿ 7.63 (5H, m, 5 x ArH)
20	1795, 1750	(CCl_4): 3.72 (1H, d, J = 18 Hz, $>C<^{H}_{\underline{H}}$), 4.28 (1H, d, J = 18 Hz, $>C<^{H}_{\underline{H}}$), 4.73 (1H, d, J = 9 Hz, 4-H), 5.20 (2H, s, $C\underline{H}_2Ph$), 6.07 (1H, dd, J = 9 and 16 Hz, $\underline{H}>=<^{H}_{Ph}$), 6.75 (1H, d, J = 16 Hz, $H>=<^{H}_{Ph}$), 7.35 (10H, br s, 10 x ArH)
21 trans	1765, 1750	(CCl_4): 3.73 (1H, d, J = 18 Hz, $>C<^{H}_{\underline{H}}$), 4.12 (1H, d, J = 18 Hz, $>C<^{H}_{\underline{H}}$), 4.37 (1H, dd, J = 2.2 and 9 Hz, 4-H), 5.07 (2H, s CH_2Ph), 6.22 (1H, dd, J = 9 and 16 Hz, $\underline{H}>=<^{H}_{Ph}$), 6.68 (1H, d, J = 16 Hz, $H>=<^{H}_{Ph}$), 7.07 ∿ 7.63 (15H, m, 15 x ArH)

Table 3 Synthesis of β-Lactams (22 ∿ 25) by Phospate Anhydride-Imine Method



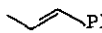
Compound	R^1	R^2	R^3	R^4	yield (%)	mp (°C)	Formula	MS m/e (M^+)	Anal. (Found) C	H	Calcd. N
22 trans	Ph	H	Ph	Et	48.9	61 ∿ 62°	$C_{19}H_{19}NO_3$	264 (M^+-45)	73.76 (74.11)	6.19 (6.25)	4.53 (4.50)
23 trans	Ph	H		Et	69.2	oil	$C_{21}H_{21}NO_3$	335			
24 trans	Cl	H	Ph	Et	3.8	oil	$C_{13}H_{14}NO_3Cl$	267, 269			
25 trans	SPh	H		Et	4.5	oil	$C_{21}H_{21}NO_3S$	367			

Table 4 Spectral Data of the β-Lactams (22 ∿ 25)

Compound	IR ($CHCl_3$) cm^{-1}	NMR (δ)
22 trans	1760, 1735	(CCl_4): 1.27 (3H, t, J = 7 Hz, $OCH_2\underline{CH_3}$), 3.40 (1H, d, J = 18 Hz, $>C<^{\underline{H}}_{H}$), 4.06 (1H, d, J = 2 Hz, 3-H), 4.25 (2H, q, J = 7 Hz, $OCH_2\underline{CH_3}$), 4.46 (1H, d, J = 18 Hz, $>C<^{\underline{H}}_{H}$), 4.76 (1H, d, J = 2 Hz, 4-H), 7.30 (10H, s, 10 x ArH)
23 trans	1750, 1735	(CCl_4): 1.30 (3H, t, J = 7 Hz, $OCH_2\underline{CH_3}$), 3.66 (1H, d, J = 18 Hz, $>C<^{\underline{H}}_{H}$), 4.12 (1H, d, J = 2 Hz, 3-H), 4.23 (2H, q, J = 7 Hz, $OCH_2\underline{CH_3}$), 4.26 (1H, d, J = 18 Hz, $>C<^{\underline{H}}_{H}$), 6.20 (1H, dd, J = 15 and 8 Hz, $\underline{H}>=<^{H}_{Ph}$), 6.67 (1H, d, J = 15 Hz, $H>=<^{\underline{H}}_{Ph}$), 7.30 (10H, s, 10 x ArH)
24 trans	1780, 1750	(CCl_4): 1.30 (3H, t, J = 7 Hz, $OCH_2\underline{CH_3}$), 3.43 (1H, d, J = 18 Hz, $>C<^{\underline{H}}_{H}$), 4.16 (2H, q, J = 7 Hz, $OCH_2\underline{CH_3}$), 4.30 (1H, d, J = 18 Hz, $>C<^{H}_{\underline{H}}$), 4.50 (1H, d, J = 2 Hz, 4-H), 4.83 (1H, d, J = 2 Hz, 3-H), 7.36 (5H, s, 5 x ArH)
25 trans	1760, 1740	($CDCl_3$): 1.23 (3H, t, J = 7 Hz, $OCH_2\underline{CH_3}$), 3.72 (1H, d, J = 18 Hz, $>C<^{\underline{H}}_{H}$), 4.15 (1H, d, J = 18 Hz, $>C<^{H}_{\underline{H}}$), 4.18 (2H, q, J = 7 Hz, $OCH_2\underline{CH_3}$), 4.41 (1H, dd, J = 2 and 9 Hz, 4-H), 6.22 (1H, dd, J = 9 and 16 Hz, $\underline{H}>=<^{H}_{Ph}$), 6.76 (1H, d, J = 16 Hz, $H>=<^{\underline{H}}_{Ph}$), 7.20 ∿ 7.80 (10H, m, 10 x ArH)

EXPERIMENTAL

Melting points were determined on a Yanagimoto hotstage apparatus. Ir and nmr spectra were measured with a Hitachi 215 spectrophotomer and a JNM-PMX-6 spectrometer (tetramethylsilance as an internal standard), respectively.

4-Substituted 1-Ethoxycarbonylmethyl-3,3-diphenyl-2-azetidinones (12 ∿ 14). —— To a solution of ethyl N-benzylideneglycinates (7 ∿ 9) (3.16 mmol) in dry benzene (50 ml) was added diphenyl ketene, which was prepared by stirring diphenylacetyl chloride (4.34 mmol) during 1 h under nitrogen atmosphere at room temperature and the mixture was further stirred overnight under the same conditions. After evaporation of the solvent, the residue was recrystallised from ethanol to give 12 - 14.

4-Substituted 1-Ethoxycarbonylmethyl-3-phthaloylimino-2-azetidinones (15 ∿ 17). —— To a mixture of the N-benzylideneglycinates (7 ∿ 9) (2 mmol) and triethylamine (6 mmol) in dry methylene chloride (150 ml) was added a solution of N-phtaloylglycyl chloride (2.4 mmol) in dry methylene chloride (50 ml) under stirring and nitrogen atmosphere at 0°C and the resulting mixture was stirred for 20 h at room temperature, then washed with water and dried (Na_2SO_4). After evaporation of the solvent, the residue was crystallised from ethanol to give the cis-isomers of 15 ∿ 17 as crystals. The mother liquid was concentrated and subjected to chromatography on silica gel eluting with n-hexane-ethyl acetate (1 : 1 v/v) to afford the trans-isomers of 15 ∿ 17 as a pale yellowish oil.

3,3-Dichloro-1-ethoxycarbonylmethyl-4-phenyl-2-azetidinone (18). —— To a mixture of ethyl N-benzylideneglycinate (7) (298 mg, 1.56 mmol) and triethylamine (189 mg, 1.87 mmol) in dry methylene chloride (20 ml) was added a solution of dichloroacetyl chloride (276 mg, 1.87 mmol) in dry methylene chloride (10 ml) under ice-cooling and stirring. The mixture was further stirred for 1 h, then washed with a brine and dried (Na_2SO_4). Evaporation of the solvent gave a brownish oil, which was purified by chromatography on silica gel eluting with n-hexane-ethyl acetate to give 18 (105 mg, 26.8 %) as an oil.

3-Substituted 1-Alkoxycarbonylmethyl-4-styryl-2-azetidinones (19 ∿ 21). —— A

mixture of the esters of glycinates (2.03 mmol) and cinnamic aldehyde (2.03 mmol) in dry carbon tetrachloride (20 ml) was stirred for 1 h at room temperature. After drying ($MgSO_4$), the resulting solution of imines (10 ∿ 11) was diluted with dry methylene chloride to 250 ml. After addition of triethylamine (2.84 mmol), a solution of the acid chlorides (2.44 mmol) in dry methylene chloride (50 ml) was added to the above mixture within 3 h under ice-cooling and the resulting mixture was stirred for 30 min, washed with a brine and dried (Na_2SO_4). Evaporation of the solvent, followed by purification with silica gel column chromatography gave 19 ∿ 21.

General method using Diethylphosphorochloridate. —— After stirring a mixture of the carboxylic acids (4 ∿ 6) (8 mmol) and diethylphosphorochloridate (8 mmol) in dry methylene chloride (40 ml) for 20 min at room temperature, a solution of the imines (7, 10) (8 mmol) and triethylamine (1.6 mmol) in methylene chloride was added dropwise to the above mixture during 2 h at the same temperature under stirring. The mixture was further stirred for 15 ∿ 20 h, washed with water and dried (Na_2SO_4). Evaporation of the solvent, followed by purification with silica gel column chromatography eluting with n-hexane-ethyl acetate (20 : 1 v/v) gave 22 ∿ 25.

1. Part 774: T. Kametani, et al., Heterocycles, in press.
2. A. K. Mukerjee and R. C. Srivastava, Synthesis, 1973, 327.
3. P. G. Sammes, Chem. Rev., 1976, 76, 113.
4. A. K. Bose and B. Anjaneyulu, Chem. and Ind., 1966, 903.
5. A. K. Bose, B. Anjaneyulu, S. K. Bhattacharya, and M. S. Manhas, Tetrahedron, 1967, 23, 4769.
6. M. S. Manhas and A. K. Bose, Synthesis of Penicilin, Cephalospolin C, and Analogs, Marcel Dekker Inc., New York, 1969.
7. A. K. Bose, J. C. Kapur, J. L. Fahey, and M. S. Manhas, J. Org. Chem., 1973, 38, 3437.
8. A. K. Bose and J. L. Fahey, J. Org. Chem., 1974, 39, 115.
9. M. S. Manhas, B. Lal, S. G. Amin, and A. K. Bose, Synth. Comm., 1976, 6, 435.
10. M. D. Bachi and M. Rothfield, J. C. S. Perkin I, 1972, 2326.
11. E. C. Taylor, A. McKillop, and G. H. Hawks, Org. Synth., 1972, 52, 36.

Received, 22nd December, 1978