STUDIES ON THE SYNTHESES OF HETEROCYCLIC COMPOUNDS AND NATURAL PRODUCTS. PART 1007. SYNTHETIC STUDIES ON CEPHALOSPORIN DERIVATIVES : AN EFFECTIVE AMIDE FORMATION REACTION

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Abstract —— An effective amide formation reaction at the C_7-position of 7-aminocephalosporanic acid benzhydryl ester has been achieved by the adoption of Mukaiyama's procedure with a slight modification.

The syntheses of various types of cephalosporin derivatives from 7-aminocephalosporanic acid (7-ACA) by the modification of an amino group at the C_7-position with the formation of amide linkage, have widely been investigated for the purpose of discovery of new semi-synthetic β-lactam antibiotics. Though acid chlorides or their acid anhydrides have been employed, in general, as acylating reagents to obtain the corresponding amide from 7-ACA, those acylation sometimes afforded none or a trace of the desired products. For example, the treatment of 7-aminocephalosporanic acid benzhydryl ester (1) with pyridylthioacetyl chloride or its anhydride afforded a trace of the desired product[1], cephapirin benzhydryl ester (< 5 %).

It has been known that the utilization of 2-chloro-1-methylpyridinium halides as activating reagents of a carboxyl group, developed by Mukaiyama[2-7] has provided an effective method for the formation of various types of amide or ester linkages.

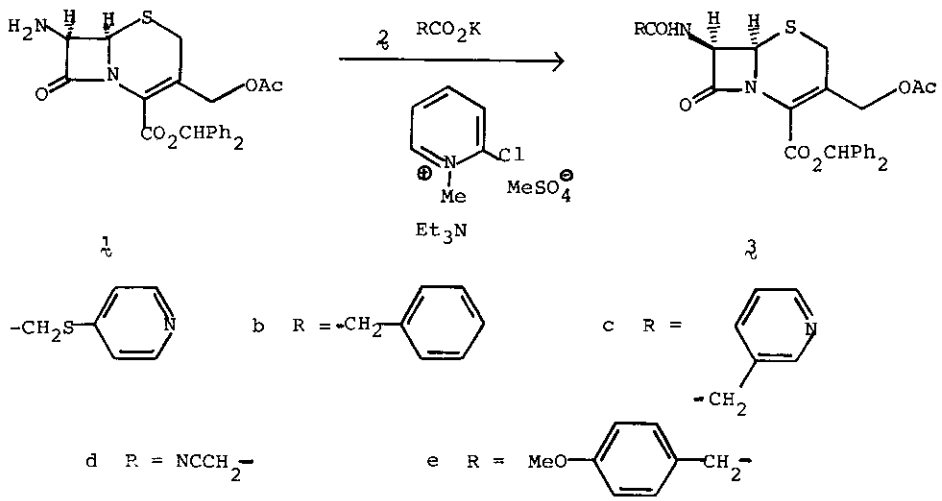
An application of the above procedure, which requires 2 equimolar amounts of triethylamine for the synthesis of cephalosporin derivatives, however bring about an isomerization of the Δ^3-double bond to Δ^2-derivative with a formation of an amide linkage at the C_7-position[8]. Therefore development of an effective amide formation reaction for 7-ACA derivative without an isomerization of Δ^3-double bond will be desirable. We here wish to report a sufficient and convenient amide formation reaction for 7-ACA derivative employing Mukaiyama's procedure with a slight modification.

Among the various attempts, the treatment of 7-ACA benzhydryl ester with potassium

pyridylthiocarboxylate in the presence of 1 equimolar amount of triethylamine and 2-chloro-1-methylpyridinium methyl sulfate as an activating reagent has been deduced to be an optimum reaction condition to give cephapirin benzhydryl ester (3a) in 86 % yield. This reaction was successfully applied to the synthesis of several cephalosporin derivatives, and the results are summarized in Table.†

The potassium salts of 3-pyridylacetic acid and cyanoacetic acid also gave the desired products (2c and 2d) in moderate yields. Since we have already published[9] the convenient deblocking procedure of cephalosporin benzhydryl esters, the above amide formation reaction would provide a useful pathway to the synthesis of various types of cephalosporin derivatives.

Table The amide formation reaction of 7-ACA benzhydryl ester (1)



Acylating Reagent	Product	M.p. (°C)	Yields (%)
2a	3a	108 - 114	86
2b	3b	140 - 143 (decomp.)	83
2c	3c	137 - 141	56
2d	3d	163 - 167 (decomp.)	69
2e	3e	99 - 101	67

† Δ^2-Isomers could not be isolated under this reaction condition.

EXPERIMENTAL SECTION

Melting points are not corrected. IR spectra were measured with a Hitachi 260 - 10 spectrophotometer, NMR spectra with JEOL PMX-60 and JEOL JNM-FX 100 spectrometers (tetramethylsilane as internal reference).

2-Chloro-1-methylpyridinium Sulfate —— To a refluxed solution of dimethyl sulfate (50.4 g) in dichloroethane (60 ml) was added a solution of 2-chloropyridine (45.8 g) in dichloroethane (40 ml) over the period of 20 min, and the resulting mixture was further heated at reflux for 2 h. After cooling to room temperature, the solution was diluted with methylene chloride to 300 ml of volume of the solution (95.8 g / 300 ml), which was used to the following reaction.

General Procedure for the Amide Formation Reaction —— To a stirred solution of the potassium carboxylate (2a-c, 5 mmol) and 7-ACA benzhydryl ester (1.5 mmol) in methylene chloride (12 ml) were added 2-chloro-1-methylpyridinium methyl sulfate (4.5 ml) and triethylamine (5 mmol), respectively, as in the presence of a slightly excess of the pyridinium salt at ambient temperature over the period of 20 min. After the stirring for 0.5 h, the mixture was treated with ethyl acetate (10 ml). The organic layer was washed with water, dried (Na_2SO_4) and evaporated to give the residue, which was crystallized from n-hexane-ether.

Cephapirin Benzhydryl Ester (3a) : IR ν_{max}^{KBr} cm^{-1} : 3270 (NH), 1780, 1740, 1720 (sh), 1660 (C=O); NMR ($CDCl_3$) δ : 2.00 (3H, s, OAc), 3.24 (1H, d, J = 17Hz, C_2-H), 3.48 (1H, d, J = 17Hz, C_2-H), 3.75 (2H, s, S-C$\underline{H}_2$CO), 4.72 (1H, d, J = 13Hz, C$\underline{H}$HOAc), 4.92 (1H, d, J = 5Hz, C_6-H), 5.02 (1H, d, J = 13Hz, CH$\underline{H}$OAc), 5.80 (1H, dd, J = 5 and 10Hz, C_7-H), 6.95 (1H, s, C$\underline{H}$Ph$_2$), 7.10 - 7.18 (2H, m, pyridine protons), 7.20 - 7.52 (11H, Ar$\underline{H}$ and N$\underline{H}$), 8.40 - 8.52 (2H, m, pyridine protons). Anal. calcd for $C_{30}H_{27}N_3O_6S_2$: C, 61.10; H, 4.62; N, 7.13. Found : C, 60.95; H, 4.95; N, 7.04 %.

(3b) : IR ν_{max}^{KBr} cm^{-1} : 3280 (NH), 1780, 1745, 1715, 1655 (C=O); NMR ($CDCl_3$) δ : 2.00 (3H, s, OAc), 3.30 (1H, d, J = 17Hz, C_2-H), 3.50 (1H, d, J = 17Hz, C_2-H), 3.64 (2H, s, C$\underline{H}_2$Ph), 4.72 (1H, d, J = 13Hz, C$\underline{H}$HOAc), 4.94 (1H, d, J = 5Hz, C_6-H), 5.02 (1H, d, J = 13Hz, CH$\underline{H}$OAc), 5.82 (1H, dd, J = 5 and 10Hz, C_7-H), 6.02 (1H, br d, J = 10Hz, NH), 6.90 (1H, s, C$\underline{H}$Ph$_2$), 7.20 - 7.40 (15H, m, Ar$\underline{H}$). Anal. calcd for $C_{31}H_{28}N_2O_6S \cdot 0.5H_2O$: C, 65.82; H, 5.17; N, 4.95. Found : C, 65.87; H, 5.01; N, 4.93 %.

(3c) : IR ν_{max}^{KBr} cm^{-1} : 3280 (NH), 1780, 1750, 1720, 1660 (C=O); NMR ($CDCl_3$) δ : 2.00 (3H, s, OAc), 3.30 (1H, d, J = 17Hz, C_2-H), 3.56 (1H, d, J = 17Hz, C_2-H), 3.60

(2H, s, $C\underline{H}_2Py$), 4.78 (1H, d, J = 13Hz, $C\underline{H}HOAc$), 4.94 (1H, d, J = 5Hz, C_6-H), 5.04 (1H, d, J = 13Hz, $CH\underline{H}OAc$), 5.80 (1H, dd, J = 5 and 10Hz, C_7-Hz), 6.38 (1H, br d, J = 10Hz, NH), 6.92 (1H, s, $C\underline{H}Ph_2$), 7.18 - 7.40 (1H, m, Ar$\underline{H}$ and pyridine proton), 7.50 - 7.70 (1H, m, pyridine proton), 8.40 - 8.56 (2H, m, pyridine protons). Anal. calcd for $C_{30}H_{27}N_3O_6S \cdot 0.5H_2O$: C, 63.59; H, 4.98; N, 7.42. Found : 63.93 ; H, 4.78; N, 7.44 %.

(3d) : IR ν_{max}^{KBr} cm^{-1} : 3300 (NH), 2260 (CN), 1775, 1740, 1735 (sh), 1675 (C=O); NMR ($CDCl_3$) δ : 2.00 (2H, s, OAc), 3.32 (1H, d, J = 20Hz, C_2-H), 3.34 (2H, s, CH_2CN), 3.58 (1H, d, J = 20Hz, C_2-H), 4.80 (1H, d, J = 13Hz, $C\underline{H}HOAc$), 5.00 (1H, d, J = 5Hz, C_6-H), 5.06 (1H, d, J = 13Hz, $CH\underline{H}OAc$), 5.78 (1H, dd, J = 5 and 10Hz, C_7-H), 6.82 (1H, br d, J = 10Hz, N$\underline{H}$), 6.96(1H, s, $C\underline{H}Ph_2$), 7.20 - 7.48 (10H, m, Ar$\underline{H}$). Anal. calcd for $C_{26}H_{23}N_3O_6S \cdot 0.33H_2O$: C, 61.04; H, 4.66; N, 8.22. Found : C, 61.08; H, 4.55; N, 8.10 %.

(3e) : IR ν_{max}^{KBr} cm^{-1} : 3270 (NH), 1780, 1740, 1720, 1660 (C=O); NMR ($CDCl_3$) δ : 2.00 (3H, s, OAc), 3.26 (1H, d, J = 20Hz, C_2-H), 3.50 (1H, d, J = 20Hz, C_2-H), 3.54 (2H, s, $C\underline{H}_2Ar$), 3.76 (3H, s, OMe), 4.65 (1H, d, J = 14Hz, $C\underline{H}HOAc$), 4.90 (1H, d, J = 5Hz, C_6-H), 4.96 (1H, d, J = 14Hz, $CH\underline{H}OAc$), 5.88 (1H, dd, J = 5 and 10Hz, C_7-H), 5.90 (1H, br d, J = 10Hz, NH), 6.76 - 6.96 (2H, m, Ar$\underline{H}$), 6.86 (1H, s, $C\underline{H}Ph_2$), 7.00 - 7.40 (12H, m, Ar$\underline{H}$). Anal. calcd for $C_{32}H_{30}N_2O_7S$: C, 65.51; H, 5.15; N, 4.78. Found : C, 65.12; H, 5.07; N, 4.82 %.

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