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DIETHYL CHLOROPHOSPHATE: AN EFFECTIVE AND CONVENIENT COUPLING REAGENT OF CEPHALOSPORIN DERIVATIVES

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Abstract : A coupling reagent, diethyl chlorophosphate (DECP) **2**, was reacted with 2-(2-amino-4-thiazolyl)-2-*syn*-alkoxyiminoacetic acid **1** to give an active ester intermediate **3.**

Acylations by a large variety of coupling methods have been developed over the past years. Further developments in the amide synthesis of more complex β-lactam antibiotics require a new reagent[1] in order to avoid the formation of undesired side product[2,3] and to facilitate purification. Also, an acylation is one of the most important reactions which are frequently used in the synthesis of β-lactam antibiotics, and a considerable progress has been made in the developments of various methods in mild condition. It has been well known that the utilization of 1-hydroxybenzotriazole (HOBT) as an activating reagent of carboxylic acid has provided an useful method for the formation of semisynthetic cephalosporins. However, because of side reaction[4] and purification problem, various coupling reagents have been developed such as *p*-toluene sulfonyloxy-

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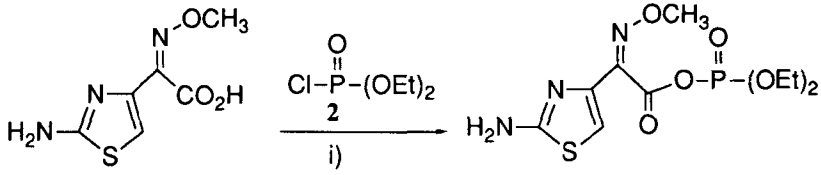
benzotriazole,[5] 1,1-*bis* [benzotriazol-yl] carbonate,[7] benzotriazolyl diethyl-phosphate[8] and have been widely used in the preparation of cephalosporin.[9] But these coupling reagents required a comparatively long reaction time.[10] As a contribution in this field, we described here the use of diethyl chlorophosphate(DECP) for a formation of the active ester intermediated **3**. The new condensing reagent **2** is a stable compound, during storage, soluble in most of organic solvents, readily accessible, commercially available and inexpensive even in large amount. The crucial step of the present appoach was the reaction between a carboxylic acid and DECP, which gives an entirely new product, the highly reactive acyloxy diethyl enol phosphate instead of the acyl chlorides.[4]

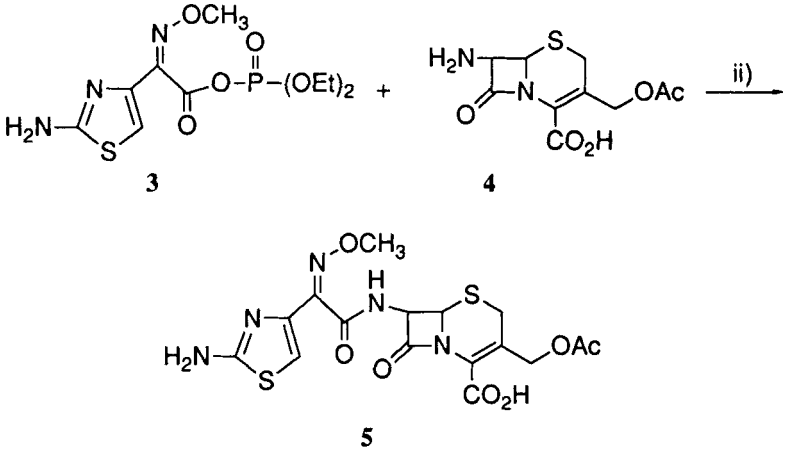


Reagent and Condition: i) Et_3N, CH_3CN, 0~5°C, 2 h.

Scheme 1

In order to demonstrate the simplicity and versatility, DECP **2** was directly reacted with 2-(2-amino-4-thiazolyl)-2-*syn*-methoxyimino acetic acid **1** (ATA) with unprotected amino group and even with unprotected N-hydroxy group. The acylation of the carboxylic acid of ATA **1** was carried out successfully by the treatment of one equivalent DECP **2** in the presence of organic or inorganic base to afford the active ester intermediate **3**. The active ester intermediate **3** was easily isolated by usual work-up and identified by the spectroscopic properties. The best results in the activation stage were achieved by adding N,N-diisopropyl ethyl amine dropwise to the solution of ATA **1** and DECP **2** in appropriate inert

solvents such as dichloromethane, acetonitrile, chloroform, tetrahydrofuran, and N,N-dimethylformamide at 0~5 °C. Monitoring of the reaction by HPLC and TLC showed that the formation of the reactive intermediate **3** was usually completed within 2~4 h except the functionalized N-hydroxyaminothiazole acetic acid in which case a reaction time of 6~7 h was required. The active ester intermediate **3** was usually a crystalline material, except N-hydroxyaminothiazole active ester. They were a very stable compound which could be stored for several months at room temperature. The active ester intermediate **3** was easily handled and carried out the reaction in various organic solvents. To determine the optimum condition, we studied first the synthesis of active ester intermediate **3** (Scheme 1).

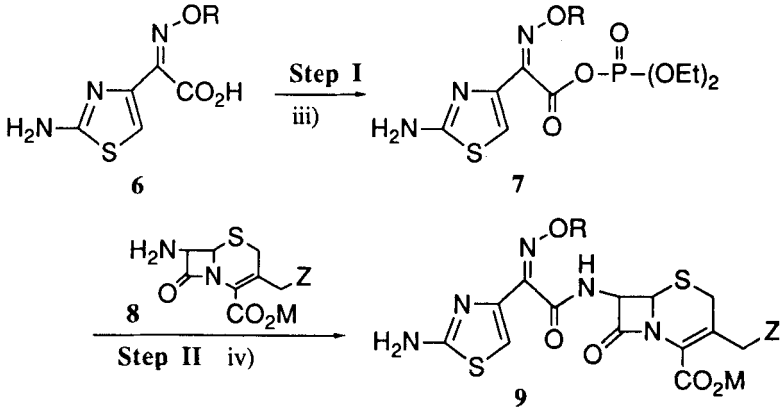


Reagent and Condition: ii) Et_3N, CH_3CN, 0°C~ rt, 2 h.

Scheme **2**

ATA **1** was dissolved in polar solvents such as THF, acetonitrile, DMF and then activated by DECP **2** in the presence of various organic bases. The effect of

solvent, base and mole ratio of reactants was studied. As shown in Table I, the best yield was obtained when 1.1 equivalent of DECP **2** was employed in DMF in the presence of N,N-diisopropylethylamine (*i*-Pr_2NEt) (Table 1, entry 8). Then the active ester intermediate **3** was treated with 7-ACA derivative **4**. The acylation is accomplished in several hours (2~7 h) to give the acylated cephalosporin derivative **5** (Scheme 2). The pure acylated cephalosporin derivative **5** was obtained after washing the reaction mixture with diluted acid and then with saturated sodium hydrogen carbonate solution. This convenient and efficient purification was made possible by the use of moderately acidic property of the diethyl phosphoric acid. A Simple extraction with basic solution easily removed the co-product, diethyl phosphoric acid, and side product as well as unreacted starting material, ATA **1**.



6 **7** **8** **9**

Reagent and Condition : iii) *i*-Pr_2NEt, DMF, 0°C~5°C, 2~4 h ;
iv) Et_3N, DMF, 0°C~rt, 2~7 h.

Scheme **3**

The activation reactions (Step I) were completed within 2~4 h at 0~5 °C temperature and the acylation reactions (Step II) ware accomplished within 2~7h

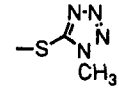
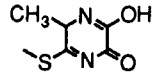
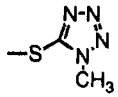
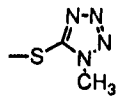
Table I. Preparation of active ester intermediate **3** under various conditions.[a)]

Entry	Mole ratio ATA **1**	Base	DECP **2**	Solvent	Base	Yield[e)](%)
1	1	1.2	1.1	CH_3CN	Pyridine	74
2	1	1.2	1.1	CH_2Cl_2	Pyridine	72
3	1	1.2	1.1	CH_3CN	Et_3N	80
4	1	1.2	1.1	CH_2Cl_2	Et_3N	77
5	1	1.2	1.1	CH_3CN	*i*-Pr_2NEt[c)]	85
6	1	1.2	1.1	CH_2Cl_2	*i*-Pr_2NEt	82
7	1	1.5	1.5	CH_3CN	*i*-Pr_2NEt	80
8	1	1.2	1.1	DMF[b)]	*i*-Pr_2NEt	88
9	1	1.5	1.5	DMF	*i*-Pr_2NEt	84
10	1	1.2	1.5	THF	*i*-Pr_2NEt	80
11	1	1.2	1.1	THF	NMM[d)]	77
12	1	1.2	1.1	DMF	NMM	82
13	1	1.5	1.5	CH_2Cl_2	NMM	80

a) Activation reaction is carried out at 0~5 °C temperature for 2~4h using 10 mmol of DECP **2** in 50 ml solvent, b) N,N-Dimethylforamide,
c) N-Diisopropylethylamine, d) N-Methylmorpholine,
e) Isolated yield base on active ester intermediate **3** used.

by adding **8** stirring in an ice-bath and then at room temperature. The desired products **9** were isolated in the ordinary manner [10a)]. These reaction conditions have been applied to the preparation of several cephalosporins containing various N-substituted oxime imino-2-aminothiazolyl groups at C-7 position and the results were summarized in Scheme 3 and Table I.

Table II. Preparation of cephalosporin derivatives **9** by an active ester intermediate **7**.

Entry	R	Z	M	Rxn. Time[a] (h)	Yield[b] (%)
1	H	-OAc	H	7.0	58.2
2	CH_3	-OAc	H	3.5	72.5
3	CH_3		H	2.5	70.3
4	CH_3		H	5.0	65.1
5	CH_3	-CH=CH_2	H	2.0	82.1
6	$CH_2CO_2{}^tBu$	-OAc	Na	2.5	84.5
7	$CH_2CO_2{}^tBu$		H	3.0	79.4
8	$CH_2CO_2{}^tBu$	-CH=CH_2	H	2.5	83.5
9	$C(CH_3)_2CO_2{}^tBu$	-OAc	H	3.0	78.4
10	$C(CH_3)_2CO_2{}^tBu$		H	4.5	80.2
11	$C(CH_3)_2CO_2{}^tBu$	-CH=CH_2	H	1.5	84.8

a) Acylation reaction condition is carried out between at ice-bath to room temperature.
b) Isolated yield base on 7-ACA derivatives **8** used.

The active ester intermediate **3** has many advantages. It is very stable compound at room temperature and easily handled as a nontoxic solid material. The acylation reaction can be carried out without undesirable side reaction to give desired cephalosporin derivatives in shorter time than coupling agents such as HOBT and HSBT.

In conclusion, we have found that DECP **2** was one of the most useful coupling reagents for the preparation of cephalosporin derivatives.

Experimental Section

All reactions were conducted under anhydrous conditions in solvents dried over molecular sieves type 4 A under nitrogen atmosphere. Melting points were determined with a Buchi capillary apparatus and uncorrected. IR spectra were taken on a Nicolet FT-IR 205 spectrometer. ^{1}H-NMR spectra were recorded on a Bruker DPX400 MHz spectrometer using TMS or sodium 2,2-dimethyl-2-silapentane-5-sulfonate (in D_2O) as an internal standrad. The coupling constants (*J*)are reported in Hz. Merck silica gel 60 (70-230 mesh) was used for column chromatography. The yields reported are for the chromatographically pure isolated products.

4-(Diethylphosphoryl)-2-(2-amino-4-thiazolyl)-2-*syn*-(2-methoxyimino)acetate (3). General procedure for the preparation of compound (5). To a stirred solution of ATA **1** (5 g, 24.08 mmol) and diethyl chlorophosphate (4.31 g, 24.9 mmol) in DMF (50 ml) in an ice-bath was slowly added N,N-diisopropylethylamine (4.42 ml, 25.5mmol). The mixture was then stirred in an ice-bath for 2 hrs and ethylacetate (120 ml) added. The organic layer was washed successively with water (500 ml x 3), 10 % K_2CO_3 (50 ml), 1N HCl (50 ml), saturated $NaHCO_3$ (50 ml), and water (70 ml), then dried over $MgSO_4$ and evaporated *in vacuo*. The solid residue was recrystallized from ethylacetate and petroleum ether to afford a off-white solid **3** : yield 7.37 g, 88 %; mp 117~119 °C; IR (KBr, cm^{-1}) 1780, 1745; ^{1}H NMR ($CDCl_3$) δ 1.36 (6H, m, CH_3 x 2), 3.95 (3H, s, OCH_3), 4.25 (4H, m, OCH_2 x 2), 6.07 (2H, br, NH_2), 6.85 (1H, s, thiazolyl-H).

7-[(2-Amino-4-thiazolyl)-2-*syn*-(2-methoxyimino)acetamido]-3-acetoxymethyl-3-cephem-4-carboxylic acid 5. General procedure for the preparation of compounds (9) . To a stirred solution of 7-aminocephalosporanic acid **4** (2.72 g, 10.0 mmol) and triethylamine (1.3 g, 12.8 mmol) in DMF (30 ml) in an ice-bath, after 30 min stirred, added dropwise active ester intermediate **3** (3.5 g, 10 mmol) solution of DMF (20 ml). After the reaction mixture was stirred at the same temperature for 3.5 h. The reaction mixture was washed with ethylacetate (50 ml x 3), and the aqueous layer cooled in an ice-bath, added thereto with 1N HCl solution at pH 2.3~2.5, and then the precipitates were collected by filtration and then dried *in vacuo* to obtain desired product **5** : yield 3.27 g, 72.5 % ; IR (KBr, cm^{-1}) 1780, 1755; ^1H NMR (DMSO-d_6) δ 2.12 (3H, s, CH_3), 3.54 (1H, d, J=18.4Hz, SCH), 5.04 (1H, d, J=12.8Hz, CH), 5.19 (1H, d, J=4.8Hz, CH), 5.84 (1H, m, CHCO), 7.25 (2H, br, NH_2), 9.64 (1H, d, J=8.18Hz, CONH).

4-(Diethylphosphoryl)-2-(2-amino-4-thiazolyl)-2-*syn*-(2-hydroxyimino)acetate : yield 4.25 g, 67.4 %; IR (Nujol , cm^{-1}) 1780, 1750; ^1H NMR ($CDCl_3$) δ 1.32 (6H, m, CH_3 x 2), 4.31 (4H, m, OCH_2 x 2), 5.91 (1H, br, OH), 7.21 (1H, s, thiazol-H), 7.94 (2H, br, NH_2).

4-(Diethylphosphoryl)-2-(2-amino-4-thiazolyl)-2-*syn*-(2-*t*-butoxycarbonyl-methoxyimino)acetate : yield 3.47 g, 87.3 %; IR (KBr, cm^{-1}) 1780, 1750; ^1H NMR ($CDCl_3$) δ 1.46 (9H, s, *t*-Bu), 4.24 (4H, m, OCH_2 x 2), 4.62 (2H, s, OCH_2), 6.99 (1H, s, thiazol-H), 7.26 (2H, br, NH_2).

4-(Diethylphosphoryl)-2-(2-amino-4-thiazolyl)-2-*syn*-(2-*t*-butoxyisopropoxyimino)acetate : yield 4.62 g, 87.4 %; mp 180~110 °C; IR (KBr, cm^{-1}) 1780, 1755; ^1H NMR ($CDCl_3$) δ 1.31 (6H, m, CH_3 x 2), 1.36 (9H, s, *t*-Bu), 1.47 (6H,

s, CH_3 x 2), 4.21 (4H, m, OCH_3 x 2), 6.82 (1H, s, thiazol-H), 8.63 (2H, br, NH), 11.42 (1H, d, *J*=18.1Hz, CHO).

7-[2-(2-Formamido-4-thiazolyl)2-*syn*-(2-*t*-butoxycarbonyl)-acetamido]-3-vinyl-3-cephem-4-carboxylic acid : yield 3.75 g, 85%; IR (KBr, cm^{-1}) 1785, 1755, 1690; ^1H NMR ($CDCl_3$) δ 1.39 (9H, d, *J*=18.5Hz, *t*-Bu), 3.59 (1H, d, *J*=4.58Hz, SCH), 3.84 (1H, d, *J*=4.58Hz, SCH), 4.59 (2H, d, *J*=4.84Hz, CH), 5.32 (1H, d, *J*=11.8Hz, $CH=CH_2$), 5.60 (1H, d, *J*=17.8Hz, $CH=CH_2$), 5.83 (1H, m, CH), 6.89 (1H, m, $CH=CH_2$), 7.42 (1H, s, thiazol-H), 8.50 (1H, s, NH), 9.64 (1H, d, *J*=8.2Hz, CONH), 12.6 (1H, br, CHO).

7-[2-(2-Amino-4-thiazolyl)-2-*syn*-(2-*t*-butoxycarbonylmethoxyimino)-acetamido]-3-vinyl-3-cephem-4-carboxylic acid : yield 3.98 g, 83.5 %; mp>250 °C;IR (KBr, cm^{-1}) 1785, 1755, 1700; ^1H NMR (DMSO-d_6) δ 1.39 (9H, s, *t*-Bu), 3.59 (H, d, *J*=4.58Hz, SCH), 3.84 (1H, d, J=4.58, SCH), 4.56 (2H, d, *J*=4.84Hz , NCH), 5.32 (1H, d, *J*=11.8Hz, $CH=CH_2$), 5.60 (1H, d, *J*=17.8Hz, $CH=CH_2$), 5.83 (1H, m, CH), 6.89 (1H, m, $CH=CH_2$), 7.42 (1H, s, thiazol-H), 8.50 (1H, s, NH_2), 9.64 (1H, d, *J*= 8.20Hz, CONH), 12.6 (1H, br, CHO).

7-[2-(2-Amino-4-thiazolyl)-2-*syn*-(2-*t*-butoxyisopropyloxyimino)-acetamido]-3-vinyl-3-cephem-4-carboxylic acid : yield 2.78g, 80.2 %; mp> 280 °C; IR (KBr, cm^{-1}) 1785, 1760, 1755; ^1H NMR (DMSO-d_6) δ 1.54 (9H, s, *t*-Bu), 3.47 (1H, d, *J*=4.57Hz, SCH), 3.84 (1H, d, *J*=4.57Hz, SCH), 4.52 (2H, s, OCH_2), 4.92 (1H, d, *J*=11.52Hz, $CH=CH_2$), 5.02 (1H, m, CH), 5.14 (1H, d, *J*=17.5Hz, $CH=CH_2$), 5.59 (1H, m, CH), 6.85 (1H, s, thiazol-H), 7.26 (1H, m, $CH=CH_2$), 7.34 (2H, s, NH_2), 9.45 (1H, d, *J*=8.01Hz, CH).

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10. a) Ger Offen. DE 3,316,798, **1984.** b) According to this patent, in general about fifteen hours is required for completion of 7- aminocephalosporanic acid derivatives by the method of HOBT-DCC.

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