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Phosphorus in Organic Synthesis. XVI.[1] Diphenyl Phosphorazidate (DPPA) and Diethyl Phosphorocyanidate (DEPC). Two New Reagents for the Preparation of Thiol Esters from Carboxylic Acids and Thiols[2]

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Thiol esters were directly and conveniently prepared from carboxylic acids and thiols with diphenyl phosphorazidate (DPPA) or diethyl phosphorocyanidate (DEPC) in the presence of triethylamine in dimethylformamide solution. Both aromatic and aliphatic acids easily react with both aromatic and aliphatic thiols. The method can be efficiently applied to the thiol ester synthesis with little racemization, demonstrated by the formation of ethyl thiol ester of benzoyl-L-leucine.

Keywords——thiol esters; condensation; S-acylation; organophosphorus compounds; racemization test; amino acid derivatives; penicillins

Thiol esters (acyl thiols) play important roles in biological system as acyl coenzyme A, S-acetyl dihydrolipoic acid and others.[4] Although this fact has led organic chemists to investigate the chemical properties of thiol esters,[4] it is rather surprising that there have been very few generalized methods for the direct preparation of thiol esters from carboxylic acids and thiols.[4a,5]

In our previous papers of the series, diphenyl phosphorazidate ($N_3PO(OPh)_2$, DPPA)[1,6,7] and diethyl phosphorocyanidate ($NCPO(OEt)_2$, DEPC)[1,7,8], in combination with triethylamine, have been revealed to be efficient reagents for the coupling of carboxylic acids with amines. Using these organophosphorus reagents, we have succeeded in the preparation of thiol esters by direct coupling of carboxylic acids with thiols:

$$RCO_2H \xrightarrow[Et_3N]{\text{DPPA or DEPC}} \begin{cases} \xrightarrow{R'NHR''} RCONR'R'' \\ \xrightarrow{R'''SH} RCOSR''' \end{cases}$$

As preliminary experiments, 3-phenylpropionic acid was allowed to react with butanethiol using an equimolar DPPA in the presence of triethylamine in dimethylformamide to

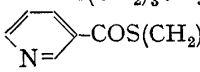
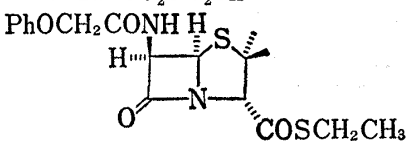
1) Part XV: Y. Hamada, S. Rishi, T. Shioiri, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **25**, 224 (1977).
2) A part of this work was preliminary communicated: S. Yamada, Y. Yokoyama, and T. Shioiri, *J. Org. Chem.*, 39, 3302 (1974).
3) Location: *7-3-1, Hongo, Bunkyo-ku, Tokyo, 113, Japan.*
4) *a*) T.C. Bruice, "Organic Sulfur Compounds," Vol. 1, ed. by N. Kharasch, Pergamon Press, New York and London, 1961, Chapter 35; *b*) T.C. Bruice and S.J. Benkovic, "Bioorganic Mechanism," Vol. 1, W.A. Benjamin, Inc., New York and Amsterdam, 1966, Chapter 3.
5) For recent examples, see Y. Watanabe, S. Shoda, and T. Mukaiyama, *Chem. Lett.*, **1976**, 741; F. Souto-Bachiller, G.S. Bates, and S. Masamune, *J. Chem. Soc. Chem. Comm.*, **1976**, 719.
6) T. Shioiri, K. Ninomiya, and S. Yamada, *J. Am. Chem. Soc.*, **94**, 6203 (1972); T. Shioiri and S. Yamada, *Yuki Gosei Kagaku Kyokai Shi*, **31**, 666 (1973); T. Shioiri and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **22**, 849, 855, and 859 (1974); K. Ozawa, T. Shioiri, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **25**, 122 (1977).
7) S. Yamada, N. Ikota, T. Shioiri, and S. Tachibana, *J. Am. Chem. Soc.*, **97**, 7174 (1975); Y. Hamada, T. Shioiri, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **25**, 221 (1977).
8) S. Yamada, Y. Kasai, and T. Shioiri, *Tetrahedron Lett.*, **1973**, 1595; T. Shioiri, Y. Yokoyama, Y. Kasai, and S. Yamada, *Tetrahedron*, **32**, 2211 (1976).

give S-butyl 3-benzenepropanethioate in 71% yield. The use of DEPC under the same reaction conditions resulted in 61% yield of the thiol ester.[9] However, the use of 2 equivalents of both DEPC and triethylamine raised the yield to 80%.

Based on these results various thiol esters were prepared according to the following general procedure: To a stirred mixture of DPPA (1 equivalent) or DEPC (2 equivalents), a carboxylic acid (1 equivalent), and a thiol (1.2 equivalents) in dimethylformamide was added triethylamine (1 equivalent in the DPPA method and 2 equivalents in the DEPC method) under ice-cooling, and the mixture was stirred at room temperature for 3 hr. As summarized in Table I, both aromatic and aliphatic carboxylic acids easily couple with both aromatic and aliphatic thiols, especially when DEPC is a condensing agent. Interestingly, a highly functionalized penicillin thiol ester was obtained by the DPPA method, but the DEPC method was proved fruitless in this particular case. The successful conversion of Z-L-Thr-OH[10] to

Table I. Preparation of Thiol Esters

$$RCOOH + R'SH \xrightarrow[Et_3N \text{ in DMF}]{\text{DEPC or DPPA}} RCOSR^{a)}$$

Thiol ester	Yield, %[b,c]	mp or bp(mm) (°C)
$PhCH_2CH_2COSCH_2CH_3$	85(75) (50)[d]	121(5)
$PhCH_2CH_2COSCH(CH_3)_2$	70	121—123(5)
$PhCH_2CH_2COS(CH_2)_3CH_3$	80(71)	125—128(5)
$PhCH_2CH_2COSC(CH_3)_3$	49	118(5)
$PhCH_2CH_2COSPh$	75(38) (91)[e]	49— 51[f]
$CH_3(CH_2)_6COSCH_2CH_3$	74(58)	90(3)[g]
$(CH_3)_3CCOSCH_2Ph$	79	114(4)
$PhCOS(CH_2)_3CH_3$	95	125(5)[h]
	87	95(1)
$CH_3CH(HO)CH(NHCO_2CH_2Ph)COSCH_2CH_3$	56(61)	106—107[i]
	Trace (51)[j]	Viscous oil
$(CH_3)_2CHCH_2CH(NHCO_2C(CH_3)_3)COSCH_2CH_3$	(82)	93— 96[k]

a) Unless otherwise stated, the reactions were performed as described in the general procedure given in the text.
b) Based on chromatographically purified materials, whose purities were checked by TLC and IR and NMR spectra.
c) Yield in parentheses were obtained using DPPA.
d) Obtained using DCCD in DMF solvent.
e) Obtained using DCCD in CH_2Cl_2.
f) Lit. mp 49 (J. Gosselck, H. Barth, and L. Béress, *Ann.*, **671**, 1 (1964)).
g) Lit. 94—96° (6 mm). (S. Okumura, M, Masumura, and T. Horie, *Yuki Gosei Kagaku Kyokai Shi*, **17**, 415 (1954); *C. A.*, **53**, 17957 *i* (1959)).
h) Lit. bp 160° (23 mm) (J. W. Kimball and E. E. Reid, *J. Am. Chem. Soc.*, **38**, 2757 (1916)).
i) $[\alpha]_D^{20}$ −57.6° (*c*=2.1, $CHCl_3$).
j) Potassium salt of phenoxymethylpenicillin (kindly donated by Dr. M. Kuramoto of Toyo Jozo Co., Ltd.) was allowed to react with 7 equiv. of ethanethiol and 2 equiv. of DPPA without triethylamine.
k) $[\alpha]_D^{20}$ −39.6° (*c*=2, $CHCl_3$).

9) This comparatively low yield may be due to the formation of tetraethyl phosphoric anhydride which may be formed by the reaction of DEPC and diethyl hydrogen phosphate, the latter of which will be produced from DEPC after the thiol ester formation.
10) Symbols and abbreviations of amino acid derivatives are in accordance with the recommendations of the IUPAC-IUB Commision on Biochemical Nomenclature, *Pure Appl. Chem.*, **40**, 315 (1974).

its ethanethiol ester makes prominent the selective nature of the process, because its hydroxyl function was inert.

N,N'-Dicyclohexylcarbodiimide (DCCD) has been known as a reagent for the preparation of aromatic thiol esters in the peptide chemistry.[11] Hence, comparisons of the DPPA and DEPC methods with the DCCD method were made.[12] As shown in Table I, the DCCD method is relatively superior to the DPPA and DEPC methods in the coupling of 3-phenylpropionic acid with benzenethiol, but far inferior in the formation of S-ethyl 3-benzenepropanethioate. After our work had been completed, Grunwell and Foerst have also reported[13] that aromatic thiols react more easily with carboxylic acids than aliphatic ones in the DCCD method.

In view of the apparent lack of the racemization during peptide synthesis including the Young racemization test[14] using both DPPA and DEPC,[7,8] the racemization during the thiol ester formation was investigated by the coupling of Bz-L-Leu-OH with ethanethiol.[15] Thus, optically pure Bz-L-Leu-SEt was prepared from Boc-L-Leu-OH. Boc-L-Leu-OH was condensed with ethanethiol by the DPPA method to give Boc-L-Leu-SEt, which was treated with hydrogen chloride in ethyl acetate to furnish the hydrochloride of H-L-Leu-SEt. Benzoylation of the hydrochloride with benzoyl chloride afforded Bz-L-Leu-SEt, mp 118—119°, $[\alpha]_D^{20}+16.8°$ ($c=3.2$, acetone), which will be definitely optically pure since the above reaction sequences do not involve any steps susceptible to racemization.[14,16]

Coupling of Bz-L-Leu-OH with ethanethiol using DPPA was investigated first on the influence of solvent. Similarly to the peptide bond formation using DPPA,[6] dimethylformamide was proven to be superior to the other solvents, as shown in Table II. Table III shows the effects of reaction temperature, time, and molar ratio of the reagents on the racemization test in dimethylformamide. As expected, the content of L-isomer increased with decreasing the coupling temperature in company with decrease of the yield. Interestingly, racemization seemed to occur more easily when an excess of ethanethiol was used. DEPC was also subjected to the racemization test under the same reaction conditions best for the DPPA method. However, DEPC was not so effective as DPPA on both the material yield and the extent of racemization. The data in Table III will suggest that the DPPA method

Table II. Solvent Effect of the Racemization Test[a]

$$\text{Bz-L-Leu-OH} + \text{EtSH} \xrightarrow[\text{Et}_3\text{N}]{\text{DPPA}} \text{Bz-Leu-SEt}$$

Solvent	Yield, (%)	mp (°C)	Bz-Leu-SEt $[\alpha]_D^{20}$ (°C)	L-Isomer (%)
DMF	83	93—103	14.2(3.03)	85
AcOEt	88	95—110	12.7(3.08)	76
THF	84	97—112	13.0(3.10)	77
CH_2Cl_2	52	93—107	11.6(3.08)	69

a) The reactions were carried out at 0° overnight using 1 equiv. of Bz-L-Leu-OH, 1.2 equiv. of DPPA, EtSH, and Et_3N, respectively.

11) See, *e.g.*, K. Loyd and G.T. Young, *J. Chem. Soc.* (*C*), **1971**, 2890.
12) When we started this work, there were no reports on the application of DCCD to the coupling of carboxylic acids with aliphatic thiols except the report on thiolactone formation: Y. Murakami, K. Koga, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **20**, 583 (1972).
13) J.R. Grunwell and D.L. Foerst, *Synth. Comm.*, **6**, 453 (1976).
14) M.W. Williams and G.T. Young, *J. Chem. Soc.*, **1963**, 881.
15) This might be called "the Young racemization test on the thiol ester formation."
16) *Cf.* M. Bodanszky, Y.S. Klausner, and M.A. Ondetti, "Peptide Synthesis," 2nd ed., John Wiley and Sons, New York, N.Y., 1976, Chapter 6.

Table III. The Racemization Test in Dimethylformamide

$$\text{Bz-L-Leu-OH} + \text{EtSH} \xrightarrow[\text{Et}_3\text{N}^{a)}]{\text{DPPA}} \text{Bz-Leu-SEt}$$

Run	DPPA[b]	EtSH[c]	React. temp. (°C)	React. time (hr)	Yield (%)	mp (°C)	Bz-Leu-SEt $[\alpha]_D^{20}$ (C)	L-Isomer (%)
1	1.2	3.5	20	3	75	91—109	13.0(2.96)	77
2	1.2	3.5	0	3	74	102—104	13.5(2.94)	80
3	1.2	3.5	−25	3	54	95—104	15.3(3.04)	91
4	1.2	1.2	0	3	74	85—110	14.0(3.05)	83
5	1.2	1.2	0	12	83	93—110	14.2(3.03)	85
6	1.2	1.2	−25	4	83	90—113	15.5(3.20)	92
			0	12				
7	1.5	1.2	−25	4	84	93—110	15.1(2.98)	90
			0	12				
8	1.5	3	−25	4	86	93—113	14.2(3.11)	85
			0	12				
9	1.2	3	−25	4	77	98—113	14.3(2.91)	85
			0	12				
10	1.2[d]	1.2	−25	4	65	93—113	14.3(2.92)	85
			0	12				

a) 1.2 Equiv. of Et_3N were used unless otherwise stated.
b) Molar ratio of DPPA/Bz-L-Leu-OH.
c) Molar ratio of EtSH/Bz-L-Leu-OH.
d) 2 Equiv. of DEPC and Et_3N were used.

may be applied to the thiol ester synthesis with little racemization. But, compared to the peptide bond formation, more attention should be paid for the reaction conditions of the thiol ester formation sensitive to racemization.

Since the direct way to thiol ester from carboxylic acids and thiols has been opened with the aid of DPPA or DEPC, the synthetic application of thiol esters is currently under way.[17]

Experimental

Melting points and boiling points were uncorrected. Silica gel (Wakogel C-200) was used for column chromatography. The organic solutions were dried over magnesium sulfate before vacuum evaporation. DPPA[6] and DEPC[8] were prepared according to our previous reports. Only a few representative procedures for the preparation of thiol esters have been described in detail. Physical, analytical and spectral data are shown in Table I—V.

S-Butyl 3-Benzenepropanethioate. (i) **With DPPA**——To a stirred mixture of 3-phenylpropionic acid (0.75 g, 5 mmol), butanethiol (0.5 g, 5 mmol), and DPPA (1.38 g, 5 mmol) in dimethylformamide (5 ml) was added triethylamine (0.50 g, 5 mmol) in dimethylformamide (5 ml) at −7——10°. The mixture was stirred at room temperature overnight. Benzene (100 ml) was added to the reaction mixture, which was successively washed with 5% aqueous citric acid, saturated aqueous sodium bicarbonate, and saturated aqueous sodium chloride, and dried. The evaporated residue was purified by a column chromatography with hexane–ethyl acetate (20: 1) to give S-butyl 3-benzenepropanethioate (0.79 g, 71%).

(ii) **With DEPC**——To a stirred mixture of 3-phenylpropionic acid (0.75 g, 5 mmol), butanethiol (0.6 ml, 5.5 mmol), and DEPC (1.63 g, 10 mmol) in dimethylformamide (5 ml) was added triethylamine (1.01 g, 10 mmol) in dimethylformamide (5 ml) at 3—5°. After the mixture was stirred at room temperature for 3 hr, the mixture was treated as in (i) to give S-butyl 3-benzenepropanethioate (0.89 g, 80%).

S-Ethyl 3-Benzenepropanethioate. (i) **With DPPA**——To a stirred mixture of 3-phenylpropionic acid (0.75 g, 5 mmol), ethanethiol (0.45 ml, 6 mmol), and DPPA (1.38 g, 5 mmol) in dimethylformamide (5 ml) was added triethylamine (0.50 g, 5 mmol) in dimethylformamide (5 ml) with ice-cooling. The mixture was

17) Related to the synthetic simulation of nonribosomal peptide biosynthesis, application of thiol esters to the peptide synthesis has been preliminary communicated: S. Yamada, Y. Yokoyama, and T. Shioiri, *Experientia*, 32, 967 (1976).

stirred at room temperature for 3 hr. Benzene (100 ml) was added to the mixture, which was successively washed with 5% aqueous citric acid, saturated aqueous sodium bicarbonate, and aqueous sodium chloride, and dried. The evaporated residue was purified by a column chromatography using hexane–ethyl acetate (20: 1) to give S-ethyl 3-benzenepropanethioate (0.73 g, 75%).

(ii) **With DEPC**——To a stirred mixture of 3-phenylpropionic acid (0.75 g, 5 mmol), ethanethiol (0.45 ml, 6 mmol), and DEPC (1.63 g, 10 mmol) in dimethylformamide (5 ml) was added triethylamine (1.0 g, 10 mmol) in dimethylformamide (5 ml) with ice-cooling. The mixture was stirred at room temperature for 3 hr, and treated as in (i) to give S-ethyl 3-benzenepropanethioate (0.83 g, 85%).

(iii) **With DCCD**——To a stirred mixture of 3-phenylpropionic acid (0.45 g, 3 mmol) and ethanethiol (0.30 ml, 4 mmol) in dimethylformamide (3 ml) was added DCCD (0.62 g, 3 mmol) in dimethylformamide (3 ml) with ice-cooling. The mixture was stirred at room temperature for 3 hr. The white precipitates were filtered and washed with benzene. The combined filtrate (*ca.* 100 ml) was treated as in (i) to give S-ethyl 3-benzenepropanethioate (0.29 g, 50%).

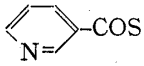
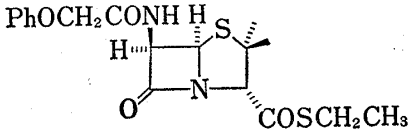
S-Phenyl 3-Benzenepropanethioate. (i) **With DPPA**——To a stirred mixture of 3-phenylpropionic acid (0.75 g, 5 mmol), benzenethiol (0.66 g, 6 mmol), and DPPA (1.38 g, 5 mmol) in dimethylformamide (5 ml) was added triethylamine (0.45 ml, 6 mmol) in dimethylformamide (5 ml) with ice-cooling. The mixture was stirred at room temperature for 3 hr. Benzene (100 ml) was added to the mixture, which was successively washed with 5% aqueous citric acid, saturated aqueous sodium bicarbonate, and saturated aqueous sodium chloride, and dried. The evaporated residue was purified by a column chromatography with hexane–ethyl acetate (20: 1) to give S-phenyl 3-benzenepropanethioate (0.46 g, 38%).

(ii) **With DEPC**——To a stirred mixture of 3-phenylpropionic acid (0.75 g, 5 mmol), benzenethiol (0.66 g, 6 mmol), and DEPC (1.63 g, 10 mmol) in dimethylformamide (5 ml) was added triethylamine (1.01 g, 10 mmol) in dimethylformamide (5 ml) with ice-cooling. The mixture was stirred at room temperature for 3 hr, and treated as in (ii) to give S-phenyl 3-benzenepropanethioate (0.91 g, 75%).

(iii) **With DCCD**——To a stirred mixture of 3-phenylpropionic acid (0.45 g, 3 mmol) and benzenethiol (0.39 g, 3.6 mmol) in methylene chloride (3 ml) was added DCCD (0.62 g, 3 mmol) in methylene chloride (3 ml) with ice-cooling. After the mixture was stirred at room temperature overnight, the resulting white precipitates were filtered and washed with diethyl ether. The combined filtrates were evaporated to the residue, which was purified as in (i) to give S-phenyl 3-benzenepropanethioate (0.66 g, 91%).

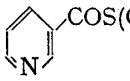
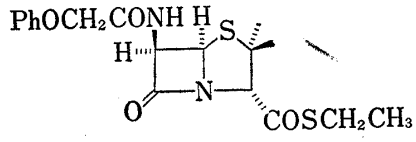
S-Butyl 3-Pyridinecarbothioate——To a stirred suspension of 3-pyridine carboxylic acid (0.62 g, 5 mmol), butanethiol (0.65 ml, 6 mmol), and DEPC (1.63 g, 10 mmol) in dimethylformamide (5 ml) was added triethylamine (1.01 g, 10 mmol) in dimethylformamide (5 ml) with ice-cooling. The resultant clear solution was stirred at room temperature for 3 hr, diluted with benzene (100 ml), and successively washed with 5% aqueous citric acid, water, saturated aqueous sodium bicarbonate, and saturated aqueous sodium chloride, and dried.

Table IV. Analytical Data

Compound	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
$PhCH_2CH_2COSCH_2CH_3$	$C_{11}H_{14}OS$	68.02	7.27		68.45	7.39	
$PhCH_2CH_2COSCH(CH_3)_2$	$C_{12}H_{16}OS$	69.21	7.74		68.75	7.79	
$PhCH_2CH_2COS(CH_2)_3CH_3$	$C_{13}H_{18}OS$	70.24	8.16		70.07	8.25	
$PhCH_2CH_2COSC(CH_3)_3$	$C_{13}H_{18}OS$	70.24	8.16		70.21	8.39	
$PhCH_2CH_2COSPh$[a]	$C_{15}H_{14}OS$	74.36	5.83		74.30	5.76	
$(CH_3)_3CCOSCH_2Ph$	$C_{12}H_{16}OS$	69.21	7.74		69.09	7.89	
$PhCOS(CH_2)_3CH_3$	$C_{11}H_{14}OS$	68.02	7.27		68.35	7.41	
	$C_{10}H_{13}NOS$	61.52	6.71	7.18	61.22	6.83	7.00
Z-L-Thr-SCH_2CH_3[b]	$C_{14}H_{19}NO_4S$	56.56	6.44	4.71	56.15	6.40	4.70
	$C_{18}H_{22}N_2O_4S_2$	54.82	5.62	7.10	54.94	5.75	7.15
Boc-L-Leu-SCH_2CH_3[c]	$C_{13}H_{25}NO_3S$	56.70	9.15	5.13	56.69	9.44	5.09
Bz-L-Leu-SCH_2CH_3	$C_{15}H_{21}NO_2S$	64.49	7.58	5.01	64.65	7.80	5.05

a) Colorless prisms (from hexane).
b) Colorless needles (from hexane).
c) Colorless prisms (from diethyl ether).

Table V. IR and NMR Spectral Data[a)]

$PhCH_2CH_2COSCH_2CH_3$	IR (f)	1690, 1455, 1265, 1050, 975, 745, 705.
	NMR (A)	1.19 (3H, t, J=7Hz, CH_3), 2.8 (6H, m, 3×CH_3), 7.08 (5H, s, C_6H_5).
$PhCH_2CH_2COSCH(CH_3)_2$	IR (f)	1685, 1455, 1245, 1050, 975, 750, 700.
	NMR (A)	1.21 (6H, d, J=7Hz, 2×CH_3), 2.8 (4H, m, 2×CH_2), 3.56 (1H, q, J=7Hz, CH), 7.08 (5H, s, C_6H_5).
$PhCH_2CH_2COS(CH_2)_3CH_3$	IR (f)	1690, 1460, 1275, 1050, 975, 750, 700.
	NMR (A)	0.90 (3H, t, J=6Hz, CH_3), 1.4 (4H, m, $CH_2(C\underline{H}_2)_2CH_3$), 2.8 (6H, m, $(CH_2)_2COSCH_2$). 7.1 (5H, m, C_6H_5).
$PhCH_2CH_2COSC(CH_3)_3$	IR (f)	1685, 1455, 1370, 1165, 1045, 970, 750, 700.
	NMR (A)	1.40 (9H, s, $C(CH_3)_3$), 2.5 (4H, m, $(CH_2)_2$), 7.1 (5H, m, C_6H_5).
$PhCH_2CH_2COSPh$	IR (d)	1695, 1440, 1170, 1160, 1035, 970, 740, 690.
	NMR (A)	2.96 (4H, s, 2×CH_2), 7.25 (10H, m, 2×C_6H_5).
$CH_3(CH_2)_6COSCH_2CH_3$	IR (f)	1695, 1460, 1265, 1130, 1053, 975.
	NMR (A)	0.88 (3H, t, J=6Hz, $C\underline{H}_3(CH_2)_6$), 1.0—1.8 (13H, m, $C\underline{H}_3CH_2S$ and $CH_3(C\underline{H}_2)_6$), 2.48 (3H, t, J=7Hz, CH_2CO), 2.8 (2H, q, J=8Hz, SCH_2).
$(CH_3)_3CCOSCH_2Ph$	IR (f)	1680, 1480, 1455, 1370, 950, 810, 770, 700.
	NMR (A)	1.17 (9H, singlet, $(CH_3)_3C$), 3.94 (2H, s, CH_2), 7.10 (5H, s, C_6H_5).
$PhCOS(CH_2)_3CH_3$	IR (f)	1660, 1450, 1200, 1175, 915, 770, 690.
	NMR (A)	0.95 (3H, t, J=7Hz, CH_3), 1.5 (4H, m, $(C\underline{H}_2)_2CH_3$), 3.00 (2H, t, J=7Hz, SCH_2), 7.4 (3H, m, $C_{3,4,5}$-H of benzene), 7.9 (2H, m, $C_{2,6}$-H of benzene).
	IR (f)	1660, 1585, 1420, 1215, 1040, 1030, 920, 815, 705.
	NMR (A)	0.94 (3H, t, J=7Hz, CH_3), 1.5 (4H, m, $(C\underline{H}_2)_2CH_3$), 3.03 (2H, t, J=7Hz, SCH_2), 7.3 (1H, m, C_5-H of pyridine), 8.65 (1H, m, C_6-H of pyridine), 9.00 (1H, d, J=3Hz, C_2-H of pyridine), 8.1 (1H, m, C_4-H of pyridine).
Z-L-Thr-SCH_2CH_3	IR (n)	3480, 3350, 1700, 1660, 1520, 1460, 1220, 1080, 1060, 750, 690.
	NMR (B)	1.20 (6H, m, 2×CH_3), 2.8 (3H, q, J=7Hz, OH and SCH_2), 4.3 (2H, m, 2×CH), 5.10 (2H, s, $C\underline{H}_2C_6H_5$), 5.92 (1H, d, J=10Hz, NH), 7.24 (5H, s, C_6H_5).
	IR (c)	3320, 1795, 1690, 1520, 1500, 1290, 1065, 840.
	NMR (B)	1.24 (3H, t, J=7Hz, CH_3CH_2), 1.52 and 1.65 (each 3H, s, 2×CH_3), 2.87 (2H, q, J=7Hz, SCH_2), 4.30 (1H, singlet, CHCOS), 4.50 (2H, s, OCH_2), 5.45 (1H, d, J=4Hz, C_7-H), 5.78 (1H, d.d., J=4Hz and 8Hz, C_6-H), 6.9 and 7.3 (6H, m, NH and C_6H_5).
Boc-L-Leu-SCH_2CH_3	IR (d)	3260, 1714, 1660, 1515, 1370, 1270, 1250, 1160, 1090, 1020, 715.
	NMR (B)	0.95 (6H, d, J=6Hz, $(C\underline{H}_3)_2CH$), 1.23 (3H, t, J=7Hz, $C\underline{H}_3CH_2$), 1.4—1.8 (3H, m, $(CH_3)_2C\underline{H}C\underline{H}_2$), 1.42 (9H, s, $(CH_3)_3C$), 2.83 (2H, q, J=7Hz, $CH_3C\underline{H}_2$), 4.3 (1H, m, $C\underline{H}NH$), 5.00 (1H, d, J=8Hz, NH).
Bz-L-Leu-SCH_2CH_3	IR (d)	3300, 1680, 1640, 1537, 1495, 1335, 1280, 1065, 725, 700.
	NMR (B)	0.95 (6H, d, J=6Hz, $(C\underline{H}_3)_2CH$), 1.23 (3H, t, J=8Hz, $C\underline{H}_3CH_2$), 1.7 (3H, m, $(CH_3)_2C\underline{H}C\underline{H}_2$), 2.88 (2H, q, J=8Hz, SCH_2), 4.9 (1H, m, CHN), 6.72 (1H, d, J=8Hz, NH), 7.4 (3H, m, $C_{3,4,5}$-H of benzene), 7.8 (2H, m, $C_{2,6}$-H of benzene).

a) IR spectra were measured either in liquid films (f), in KBr discs (d), or in $CHCl_3$ (c). NMR spectra (100 MHz) were measured either in CCl_4 (A) or $CHCl_3$ (B), and chemical shifts (δ) are given in ppm relative to internal TMS. The following abbreviations are used: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet.

The evaporated residue was purified by a column chromatography with hexane-ethyl acetate (9:1) to give S-butyl 3-pyridinecarbothioate (0.85 g, 87%).

S-Ethyl Phenoxymethylpenicillincarbothioate——To a stirred suspension of potassium phenoxymethylpenicillin (1.14 g, 3 mmol) and ethanethiol (1.5 ml, 20 mmol) in dimethylformamide (10 ml) was added DPPA (1.65 g, 6 mmol) with ice-cooling. After 30 min, the mixture became a yellow clear solution. The mixture was stirred at room temperature for 3 hr. Benzene (100 ml) was added to the mixture to give white precipitates which were filtered and washed with benzene (100 ml). The combined filtrates were washed successively with 2.5% aqueous citric acid, water, saturated aqueous sodium bicarbonate, and saturated aqueous sodium chloride, and dried. The evaporated residue was purified by a column chromatography with hexane–diethyl ether (5:1) to give S-ethyl phenoxymethylpenicillincarbothioate (0.60 g, 51%).

Synthesis of optically Pure Bz-L-Leu-SEt

Boc-L-Leu-SEt——To a stirred mixture of Boc-L-Leu-OH·H_2O (4.98 g, 20 mmol), ethanethiol (5.1 ml, 70 mmol), and DPPA (6.63 g, 24 mmol) in dimethylformamide (20 ml) was added triethylamine (2.4 g, 24 mmol) in dimethylformamide (20 ml) with ice-cooling. The mixture was stirred at room temperature for 3 hr. Benzene (500 ml) was added to the mixture, which was successively washed with 5% aqueous citric acid, saturated aqueous sodium bicarbonate, and saturated aqueous sodium chloride, and dried. The evaporated residue was purified by a column chromatography with hexane–ethyl acetate (1:9) to give Boc-L-Leu-SEt (4.50 g, 82%).

Bz-L-Leu-SEt——Boc-L-Leu-SEt (2.75 g, 10 mmol) in 2.3 N hydrogen chloride–ethyl acetate (30 ml) was kept at room temperature for 4 hr. The evaporated residue was washed with diethyl ether (50 ml) to furnish H-L-Leu-SEt·HCl (1.95 g, 94%) as colorless needles, Then an aqueous solution (25 ml) of sodium bicarbonate (2.1 g, 25 mmol) was added to a suspension of H-L-Leu-SEt·HCl (1.48 g, 7 mmol) and benzoyl chloride (1.40 g, 10 mmol) in diethyl ether (30 ml) with ice-cooling and vigorous stirring. After 1 hr, white precipitates were appeared, and ethyl acetate (10 ml) was added to the mixture to dissolve the precipitates. After the mixture was stirred for 1 hr further, the organic layer was separated and the aqueous layer was extracted with benzene (20 ml×2). The combined organic layer was washed successively with 5% aqueous citric acid and saturated aqueous sodium chloride. Drying followed by evaporation afforded a colorless solid, which was recrystallized from diethyl ether (20 ml) to give Bz-L-Leu-SEt (1.31 g, 67%) as colorless needles. Recrystallization from diethyl ether afforded an optically pure sample, mp 118—119°, $[\alpha]_D^{20}$ +16.8° (c=3.2, acetone), $[\alpha]_D^{20}$ +13.5° (c=3, ethyl acetate), $[\alpha]_D^{20}$ +4.9° (c=2, chloroform).

Racemization Test

Coupling of Bz-L-Leu-OH with Ethanethiol: Typical Procedure——To a stirred mixture of Bz-L-Leu-OH[14] (0.47 g, 2 mmol), ethanethiol (0.18 ml, 2.4 mmol), and DPPA (0.66 g, 2.4 mmol) in dimethylformamide (2 ml) was added triethylamine (0.24 g, 2.4 mmol) in dimethylformamide (2 ml) at −25°. The mixture was stirred at −20——30° for 4 hr, and then at room temperature overnight. Other various reaction conditions are described in Table II and III.

The reaction mixture was diluted with benzene (100 ml), and successively washed with 5% aqueous citric acid, aqueous saturated sodium bicarbonate, and saturated aqueous sodium chloride, and dried. The evaporated residue was purified by a column chromatography to give Bz-Leu-SEt (0.46 g, 83%). Optical purity of each product was expressed as "L-isomer, %" which was calculated by the equation: observed $[\alpha]_D^{20}$ (in acetone) × 100/+16.8° (optical rotation of pure Bz-L-Leu-SEt).