Chem. Pharm. Bull.
28(10)3140—3142(1980)

Studies on Peptides. XCIV.[1,2] Thiazoline-2-thione as a Carboxyl-activating Reagent for Peptide Synthesis

HARUAKI YAJIMA, KENICHI AKAJI, YORIKO HIROTA, and NOBUTAKA FUJII,[3]

Faculty of Pharmaceutical Sciences[3]

(Received June 9, 1980)

3-Acyl derivatives obtained from the DCC condensation of N^{α}-protected amino acids and thiazoline-2-thione were found to be useful for peptide synthesis, in the same way as active esters.

Keywords——3-acylthiazoline-2-thione derivatives of N^{α}-protected amino acids; acive N-acyl compounds in peptide synthesis; carboxyl-activating procedure in peptide synthesis; aminolysis of 3-acylthiazoline-2-thiones with amino acid esters; aminolysis of 3-acylthiazoline-2-thiones with amino acids

3-Acylthiazoline-2-thiones are useful intermediates for the preparation of aldehydes[4,5] and alcohols.[5] Of two alternative formulae for the condensation product of thiazoline-2-thione and a carboxylic acid, X-ray crystallographic examination favored formula (I),[6] instead of the thio ester (II) (Fig. 1).

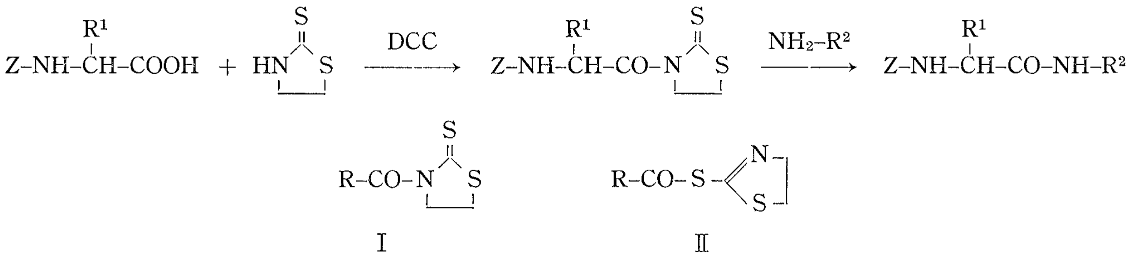

Fig. 1

We wish to report that the corresponding derivatives of N^{α}-protected amino acids are susceptible to aminolysis and consequently can be used for peptide synthesis, in the same way as active esters.[7]

Condensation of N^{α}-protected amino acids with thiazoline-2-thione by treatment with DCC[8] smoothly afforded the corresponding 3-acyl derivatives as yellowish crystalline or oily compounds, depending on the nature of the amino acids employed. These N-acyl compounds react with amino acids or amino acid esters in the presence of triethylamine at room temperature to afford the N^{α}-protected dipeptides or dipeptide esters in excellent yield (Fig. 1). The

---

1) Part XCVIII: H. Yajima, N. Fujii, Y. Hirota, Y. Nasada, Y. Hirai, and T. Nakajima, *Int. J. Pept. Prot. Res.*, in press.

2) Protected amino acids and peptides were all of the L-configuration. The following abbreviations are used: Z=benzyloxycarbonyl, Z(OMe)=*p*-methoxybenzyloxycarbonyl, Bzl=benzyl, DCC=dicyclohexylcarbodiimide, TFA=trifluoroacetic acid, DMF=dimethylformamide, Tht=thiazoline-2-thione.

3) Location: *Sakyo-ku, Kyoto, 606, Japan.*

4) T. Izawa and T. Mukaiyama, *Chem. Lett.*, **1977**, 1443.

5) Y. Nagao, K. Kawabata, and E. Fujita, *J.C.S. Chem. Comm.*, **1978**, 330.

6) R.F. Bryan, P. Hartley, S. Peckler, E. Fujita, Y. Nagao, and K. Seno, *Acta. Cryst.*, in press.

7) T. Wieland, W. Schäfer, and E. Bokelmann, *Ann. Chem.*, **573**, 99 (1951).

8) J.C. Sheehan and G.P. Hess, *J. Am. Chem. Soc.*, **77**, 1067 (1955).

progress of the reaction can be monitored by following the disappearance of the yellow color of the 3-acylthiazoline-2-thiones. Thiazoline-2-thione liberated from the reaction can be removed in most instances during recrystallization of the desired products from ether. These properties are advantageous features of this carboxyl-activating procedure.

Experimental

TLC was performed on silica gel (Kieselgel G, Merck). *Rf* values refer to the following solvent system: $CHCl_3$–MeOH–AcOH (9: 1: 0.5).

Table I. 3-Acylthiazoline-2-thiones of N^{α}-Protected Amino Acids

3-Acyl-Tht	Yield (%)	mp (°C)	$[\alpha]_D^{20}$	Formula	Analysis (%) Calcd (Found)		
					C	H	N
Z–Ala–	74	167—169	−121.5	$C_{14}H_{16}N_2O_3S_2$	51.83 (52.09	4.97 5.22	8.64 8.76)
Z–Phe–	73	127—129	−41.7	$C_{20}H_{20}N_2O_3S_2$	59.97 (60.17	5.03 5.01	7.00 6.91)
Z–Met–	69	94—96	−107.1	$C_{16}H_{20}N_2O_3S_3$	49.97 (49.69	5.24 5.38	7.29 7.09)
Z–Trp–	87	129—130	−24.4	$C_{22}H_{21}N_3O_3S_2$	60.11 (60.36	4.82 4.76	9.56 9.49)
Z(OMe)–Ala–	76	139—141	−102.5	$C_{15}H_{18}N_2O_4S_2$	50.83 (50.93	5.12 5.38	7.90 7.62)
Z(OMe)–Val–	75	124—126	−39.5	$C_{17}H_{22}N_2O_4S_2$	53.38 (53.64	5.80 5.74	7.32 7.32)
Z(OMe)–Gly–	62	115—116		$C_{14}H_{16}N_2O_4S_2$	49.39 (49.73	4.74 4.73	8.23 8.02)
ZOMe)–Asp–(OBzl)–	87	110—112	−46.8	$C_{23}H_{24}N_2O_6S_2$	56.54 (56.84	4.95 5.18	5.73 5.58)

$[\alpha]_D^{20}$ solvent; $CHCl_3$.

Table II. Protected Dipeptide Esters prepared from 3-Acylthiazoline-2-thiones

Dipeptide	Yield (%)	mp (°C)	$[\alpha]_D^{20}$	Formula	Analysis (%) Calcd (Found)		
					C	H	N
Z–Ala–Gly–OBzl[9]	83	112—114	−8.3	$C_{20}H_{22}N_2O_5$	64.85 (64.58	5.99 6.09	7.56 7.72)
Z–Phe–Gly–OMe[10]	90	119—121	−25.5	$C_{20}H_{22}N_2O_5$	64.85 (64.83	5.99 6.00	7.56 7.55)
Z–Met–Gly–OBzl	72	130—132	−11.9	$C_{22}H_{26}N_2O_5S$	61.37 (61.59	6.09 6.10	6.51 6.38)
Z–Trp–Gly–OMe[11]	72	159—161	−32.2	$C_{22}H_{23}N_3O_5$	64.53 (64.73	5.66 5.59	10.26 10.28)
Z(OMe)–Ala–Val–OMe	70	106—108	−3.6	$C_{18}H_{26}N_2O_6$	59.00 (58.74	7.15 7.36	7.65 7.93)
Z(OMe)–Val–Gly–OMe	81	138—140	−5.9	$C_{17}H_{24}N_2O_6$	57.94 (58.24	6.87 7.17	7.95 8.12)
Z(OMe)–Gly–Gly–OBzl	91	109—111		$C_{20}H_{22}N_2O_6$	62.16 (62.21	5.74 5.65	7.25 7.22)

$[\alpha]_D^{20}$ solvent; DMF.

lit. 9) mp 111—112° $[\alpha]_D^{30}$ −15.7° ($CHCl_3$).
10) mp 118—119° $[\alpha]_D^{29}$ −22.7° (DMF).
11*a*) mp 156—158° $[\alpha]_D^{22}$ −11.0±0.5° (AcOH).
11*b*) mp 158—159° $[\alpha]_D^{27}$ −11.0° (AcOH).[12]

Preparation of 3-Acylthiazoline-2-thiones of N$^{\alpha}$-Protected Amino Acids——DCC (22 mmol) was added to an ice-chilled mixture of an N$^{\alpha}$-protected amino acid (20 mmol) and thiazoline-2-thione (22 mmol) in THF (30 ml). After stirring at room temperature for 5 hr, the solution was filtered and the filtrate was concentrated. The residue was crystallized from ether or some other appropriate solvent. Some examples are listed in Table I.

Aminolysis of 3-Acylthiazoline-2-thiones——a) Preparation of Protected Dipeptide Esters: A 3-acylthiazoline-2-thione of an N$^{\alpha}$-protected amino acid (20 mmol) and Et_3N (20 mmol) were added to a stirred solution of an amino acid ester (22 mmol) in DMF (35 ml). After 12 hr, the solution was concentrated and the residue was extracted with AcOEt. The extract was washed with 5% citric acid, 5% $NaHCO_3$ and H_2O–NaCl, dried over Na_2SO_4 and concentrated. The residue was then crystallized from appropriate solvents. Some examples are listed in Table II.

b) Preparation of Protected Dipeptides: As an example, Z–Met–Gly–OH was prepared. A 3-acylthiazoline-2-thione of Z-methionine (20 mmol) in THF (40 ml) was added to a stirred solution of H–Gly–OH (22 mmol) and Et_3N (42 mmol) in H_2O (10 ml). After 12 hr, the solution was concentrated and the residue was extracted with 5%$NaHCO_3$. The extract was washed with AcOEt and then the aqueous layer was acidified with citric acid. The resulting powder was purified by batchwise washing with H_2O, followed by precipitation from MeOH with ether.: yield 4.77 g (70%), mp 130—132°, $[\alpha]_D^{20}$ $-14.8°$ ($c=0.9$, DMF), *Rf* 0.54. *Anal.* Calcd for $C_{15}H_{20}N_2O_5S \cdot 0.5H_2O$: C, 51.56; H, 6.06; N, 8.02. Found: C, 51.14; H, 5.55; N, 7.96.

---

9) G.C. Stelakatos, *J. Am. Chem. Soc.*, **83**, 4222 (1961).

10) K. Hofmann, R. Andreatta, H. Bohn, and L. Moroder, *J. Med. Chem.*, **13**, 339 (1970).

11) *a*) R. Geiger, K. Sturm, and W. Siedel, *Chem. Ber.*, **96**, 1080 (1963); *b*) K. Hofmann, M.E. Woolner, G. Spühler, and E.T. Schwartz, *J. Am. Chem. Soc.*, **80**, 1486 (1958).