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MONITORED AMINOLYSIS OF 3-ACYL-1,3-THIAZOLIDINE-2-THIONE WITH AMINO ACID AND ITS DERIVATIVE : PEPTIDE BOND FORMATION, CHEMOSELECTIVE ACYLATION, AND BRIDGING REACTION

Yoshimitsu NAGAO, Tadayo MIYASAKA, Kaoru SENO, Masahiro YAGI, and Eiichi FUJITA*

Institute for Chemical Research, Kyoto University, Uji, Kyoto-Fu 611

As a new extention of the monitored aminolysis of 3-acyl-1,3-thiazolidine-2-thione, its applications to peptide bond formation, chemoselective acylation of amino acid, and bridging reaction on the enzyme model are reported.

We developed a new method for preparation of amide through monitored aminolysis of 3-acyl-1,3-thiazolidine-2-thione (ATT).[1] Its application to the syntheses of macrocyclic diamides[2,3] and of macrocyclic spermidine alkaloids[4,5] has been reported. We now report further important utilities of this aminolysis.

MONITORED PEPTIDE BOND FORMATION We synthesized eight kinds of dipeptides and a tripeptide using this aminolysis. The accomplishment of the peptide bond formation can easily be judged by the disappearance of the original yellow color due to ATT, which is characteristic of our method and very convenient for the synthetic chemist. There have been many reports on the condensation reagents for peptide bond formation,[6] but such a nicely monitored method as ours has never been encountered.

Synthetic sequence is shown in Scheme 1. A typical example for preparation of amino acid 1,3-thiazolidine-2-thione (TT) amide 3 is as follows. Dicyclohexylcarbodiimide (DCC) (4.12 g, 20 mmol) was added to a solution of Z-L-Ala-OH 1 (4.46 g, 20 mmol) and TT (2) (2.38 g, 20 mmol) in CH_2Cl_2 (20 ml) under ice-cooling with stirring. the mixture was stirred at 0°C for 5 h and a precipitation (urea) was filtered off. Evaporation of the filtrate *in vacuo* left an oily residue, which was treated as usual to afford Z-L-Ala-TT 3a (3.94 g, 61 %) as yellow plates from $CHCl_3$-Et_2O.

Similarly, other three kinds of amides, 3b~d, were synthesized. Data on the amides 3 are summarized in Table 1.

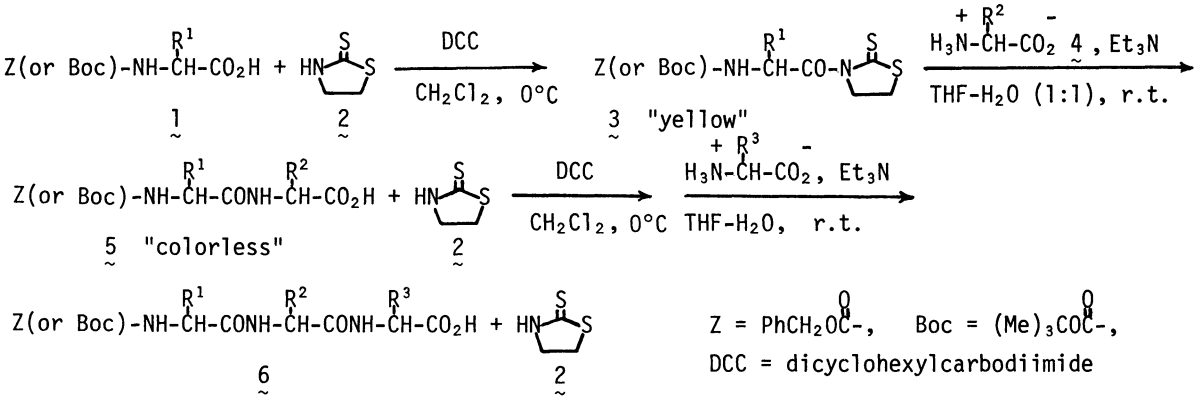
Table 1 1,3-Thiazolidine-2-thione Amide 3

amide[a] 3		yield (%)	mp (°C)	$[\alpha]_D^{t°C}$[b]	(t)
3a	Z-L-Ala-TT[c]	61	163-165	-120.0°	(17)
3b	Z-L-Met-TT	64	99-101	-97.2	(17)
3c	Z-L-Leu-TT	83	78-79	-78.4	(21)
3d	Boc-L-Phe-TT	77	168.5-170.5	-29.8	(19)

a) Satisfactory elemental analysis was obtained for each amide 3.

b) $[\alpha]_D$ was determined in $CHCl_3$ (c = 2.0).

c) TT = 



Scheme 1

Subsequently, a typical procedure for dipeptide synthesis is illustrated. A solution of glycine (4) (82.5 mg, 1.1 mmol) in water (5 ml) was added to a yellow solution of amide 3a (324 mg, 1 mmol) in THF (5 ml). After addition of Et_3N (0.2 ml, 1.5 mmol), the mixture was stirred at room temperature until original yellow color of the reaction medium varnished (1 min). The reaction mixture was condensed *in vacuo* to leave an oily residue, which was dissolved in EtOAc and washed with cold 5% HCl and brine. The organic layer, after being dried, was evaporated to leave a crude oily product, which was purified on an LH-20 Sephadex-column by MeOH to give dipeptide 5b (249 mg, 89%) as colorless fine prisms from H_2O-MeOH.

Using the similar procedure, dipeptides 5a, 5c~h, and tripeptide 6 were synthesized. All the data are collected in table 2.

Table 2 Synthesis of Peptides 5 and 6

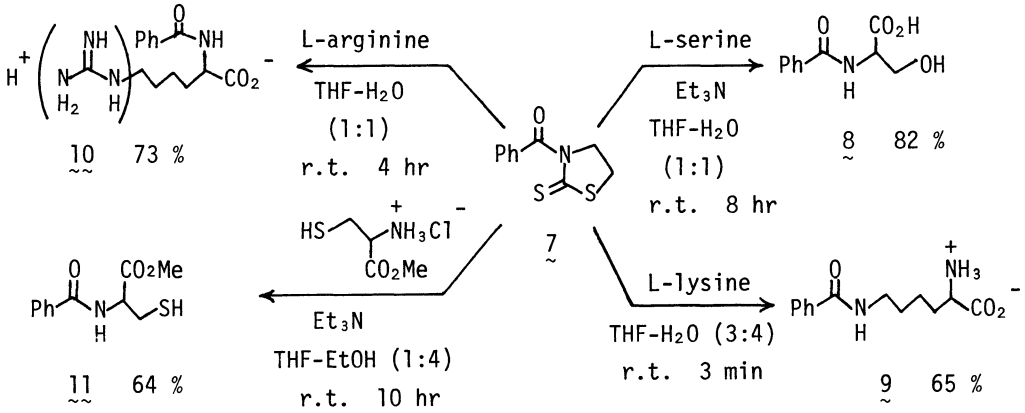
peptide[a] 5 or 6		reaction time (min)	yield (%)	mp (°C)	$[\alpha]_D^{t°C}$ (c, solvent[b], t)	
5a	Z-L-Ala-Gly-OEt	15	94	98-99	-19.7°	(1.0, E, 23)
5a	〃	80[c]	94	99-100	-22.7[d]	(1.1, E, 17)
5b	Z-L-Ala-Gly-OH	1	89	128-129	-15.4	(0.91, E, 23)
5c	Z-L-Ala-L-Ser-OH	30	88	194-196	+21.1	(0.4, DMF, 19)
5d	Z-L-Ala-L-Thr-OH	30	93	139-141	-8.2	(0.94, E, 23)
5e	Z-L-Ala-L-Phe-OH	5	87	124-126	+39.2	(0.5, DO, 21)
5f	Z-L-Met-Gly-OEt	20	88	95.5-96.5	-17.0	(0.73, E, 23)
5f	〃	110[c]	94	96-97	-19.6[e]	(1.1, E, 17)
5g	Z-L-Met-L-Phe-OH	20	95	125-126	+3.3	(1.0, E, 19)
5h	Boc-L-Phe-Gly-OH	3	93	163-164	-5.5	(0.5, DO, 21)
6	Z-L-Leu-D-Ile↓L-(S-Bzl)Cys-OH[f]	120	87	132-135	-23.5	(2.0, DMF, 19)

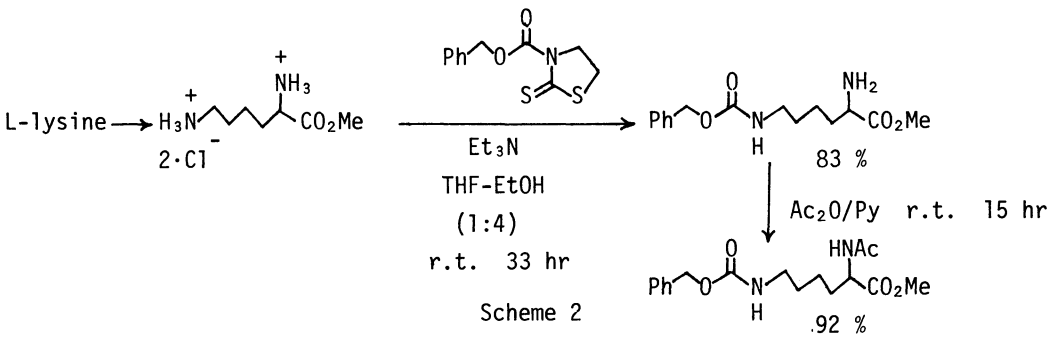
a) Elemental analyses gave satisfactory data for all peptides. b) E = ethanol, DMF = dimethylformamide, DO = dioxane. c) 1.1 Molar equiv. of Et_3N were employed. In other cases, 1.5-2.0 molar equiv. of Et_3N were used. d) Lit.[7] mp 97-98°C, $[\alpha]_D^{20}$ = -24.0°(c = 1.0, EtOH). e) Lit.[8] mp 94-96°C, $[\alpha]_D^{27}$ = -19.8°(c = 4.6, EtOH). f) Z-L-Leu-D-Ileu-OH obtained as an oily product in 89% yield from Z-L-Leu-TT and D-Ileu was converted into Z-L-Leu-D-Ileu-TT, which was allowed to react with L-(S-Bzl)Cys. The arrow mark indicates the reaction point.

Although the detailed racemization test on the synthetic dipeptides (or tripeptide) was not investigated, comparison of specific rotations of 5a and 5f with those of pure compounds reported respectively, gave a good coincidence in each case (see Table 2). The specific optical rotation ($[\alpha]_D$ -32.4°)of the dipeptide, Bz-L-Leu-Gly-OEt (85 % yield), prepared from H_2N-Gly-OEt and Bz-L-Leu-TT derived from Z-L-Leu-OH, showed 95 % optical purity, when compared with that ($[\alpha]_D$ -34.0°) of the authentic sample.[9] This new monitored procedure may be very convenient for the sequential synthesis of long-chained linear peptide, because nonprotected amino acid is available and the released TT (2) can be used recyclically.

CHEMOSELECTIVE ACYLATION A chemoselective acylation of amino acid having three (or more than three) functional groups in the molecule, is very interesting from the viewpoints of peptide synthesis and chemical modification of enzyme.

Treatments of 3-benzoyl-TT with L-serine, L-lysine, L-arginine, and L-cysteine methyl ester resulted in a chemoselective formation of the corresponding benzoyl amides 8~11,[10] respectively. Selective acylation of two types of amino groups in L-lysine was also performed (see Scheme 2).





Scheme 2

BRIDGING REACTION Bridging in an enzyme or between enzymes by particular reagent 12 or 14 having high reactivity to amino group or to amino and mercapto groups, respectively, is remarkably interesting in enzyme technology (see Fig).

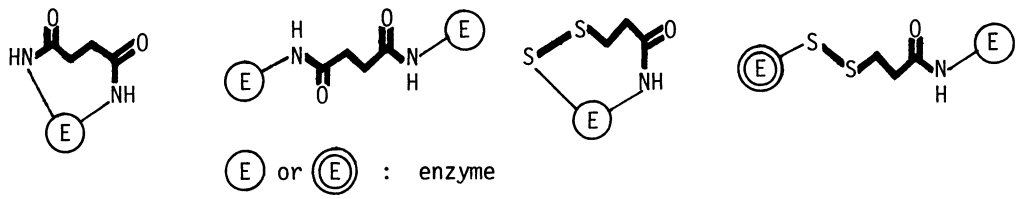
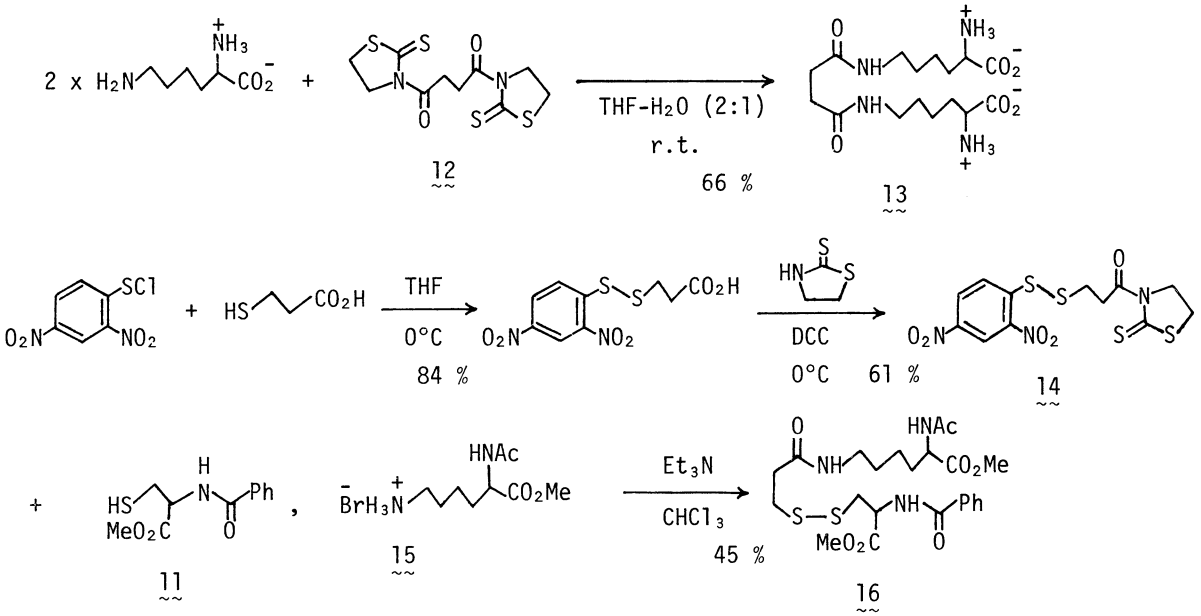


Fig. Bridging Mode of Some Reagents with Enzyme(s)

As model experiments, the following two aminolyses were carried out. On treatment with L-lysine (2 mol equiv.), butanedioic acid TT amide 12 afforded compound 13[10] in 66 % yield. A heterobifunctional reagent ("modified Carlsson type reagent"[11]) 14 prepared from 2,4-dinitrophenylsulfenyl chloride by our own method[12] was treated with equimolar amount of SH enzyme model compound 11 and another model compound 15 under the presence of Et_3N in one flask to yield the desirable product 16[10] in 45% yield (see Scheme 3). Bridging reaction with enzyme using these reagents is now in progress.



Scheme 3

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