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3-AMINOACYL-TETRAHYDROTHIAZOLE-2-THIONE AS AN ACTIVE AMIDE FOR PEPTIDE SYNTHESIS (I)[1,2]

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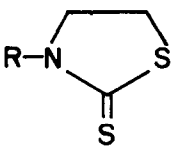
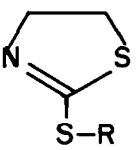
Summary: 3-Aminoacyl-tetrahydrothiazole-2-thione can be used as an active amide for peptide synthesis. A series of peptides have been synthesized with satisfactory yields by this methods.

Tetrahydrothiazole-2-thione (2-thionothiazolidine, TTT, I)[3] or the tautomeric 2-mercaptothiazoline (II) can be readily acylated to give yellow crystalline stable derivatives (III) which are soluble in most organic solvents. The structure of the acylated TTT derivatives were proven by IR, NMR and X-ray diffraction[4] to be N-Acyl-tetrahydrothiazole-2-thione (III) rather than the ester of mercaptothiazoline (IV).



(I , III)

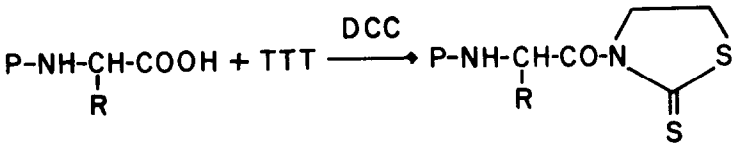


(II , IV)

(I), (II) R=H

(III), (IV) R=R-CO-

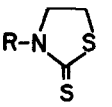
Wnen benzyloxycarbonyl or tert-butyloxycarbonyl protected amino acids are allowed to react with TTT using N,N'-dicyclohexylcarbodiimide (DCC) as condensing agent, a series of N-protected aminoacyl TTT derivatives are readily obtained:



P= $C_6H_5CH_2O$-CO- (Z) or $(CH_3)_3C$-O-CO- (Boc)

The reaction is carried out in THF, CH_2Cl_2, etc. at room temperature. Aminoacyl derivatives of TTT can also be prepared in good yield by the acid chloride or mixed anhydride method.

Table 1. Physical Properties of Some 3-Acyl and 3-N-protected Aminoacyl-TTT Derivatives*



R	m.p. °C	$[\alpha]_D^{25}$	conc. c	Solvent	Yield %
CH_3CO-	36-38				90
C_6H_5CO-	108-109				96
$C_6H_5CH_2OCO$-	81-83				95
ZGly-	120-121				81**
BocGly-	65-67				43
Hip-	148-150				34
ZAla-	162-164	-129.2°	2	DMF	78**
BocAla-	105-107	-143.7°	2	DMF	43
ZPhe	129-130	-53.0°	2	DMF	81
BocLeu-	115-120	-66.8°	2	DMF	42
t-BuO ZAsp-	94-96	-79.0°	2	DMF	40
BocTrp-	162-164	-50.6°	2	DMF	58
OBZ BocTyr	154-156	-36.0°	2	DMF	64

*All amino acids used in the present studies belonged to the L-series.

**Prepared by Ma and Zhang (ref. 1).

It is interesting to note that the specific rotations of the N-protected aminoacyl TTT derivatives (III) are greatly enhanced as compared to those of the N-protected amino acids.

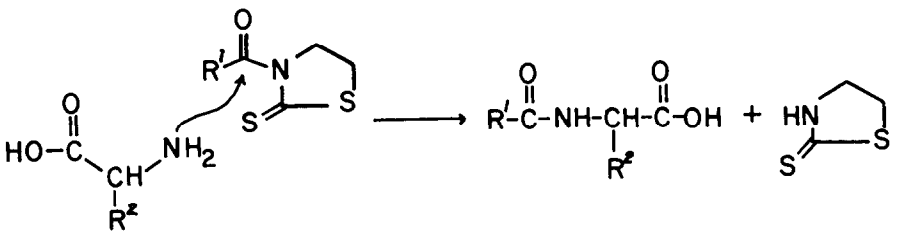
Since the 3-acyl group in III is linked to an excellent leaving group, it is an activated amide and hence should be applicable to peptide synthesis In fact, when aminoacylated TTT (III) is reacted with another amino acid component, a new peptide bond is formed smoothly with the release of (I). The reaction is generally completed in about 2-4 hours at room temperature and the yields are satisfactory, especially when the carboxyl group of the amino acid component is unprotected. Since the yellow color characteristic of compounds III gradually fade away while the aminolysis is proceeding, this color change can be used to monotor the reaction.

Table 2. Pepetides Synthesized by the TTT Method

3-Acyl-TTT	Amino Component	Product	M.P.°C	Yield %	conc. c	α_D^{25} (solvent)
PhCO-	HGlyOH	HipOH	184-188	67		
Z-	HPheOMe	ZPheOMe	180-184	82		
Hip-	HPheOMe	HipPheOMe	120-122	87		
Hip-	HPheOH	HipPheOH	176-177	70		
ZGly-	$HGlu(t\text{-}OBu)_2$	$ZGlyGlu(t\text{-}OBu)_2$	70-73	91	2	-13.6° (MeOH)*
ZGly-	HpheOH	ZGlyPheOH	126-218	66	5	+31.2° (EtOH)
ZGly-	HTyrOMe	ZGlyTyrOMe	116-118	65	2	+14.0° (EtOH)
ZGly-	HTyrOEt	ZGlyTyrOEt	117-119	60		
ZGly-	HGlyGlyOH	ZGlyGlyGlyOH	199-201	90		
ZAla-	HPheOMe	ZAlaPheOMe	98-100	89	1	-14.1° (MeOH)
ZPhe-	HGlyOEt	ZPheGlyOEt	110-112	80	2	-16.8° (EtOH)
ZGly-	HPheGlyOEt	ZGlyPheGlyOEt	118-120	90	2	-12.6° (EtOH)

*Prepared by Ma and Zhang (ref. 1).

As mentioned above, the reaction is assisted by the superior property of tetrahydrothiazole-2-thione (TTT,I) has a leaving group:



Compound (I) has been known for a long time as a copper complexing reagent and is water soluble; it can hence be removed completely from the crude product by shaking with a 15% copper sulfate solution. The product thus obtained is pure enough for catalytic hydrogenolysis.

Hydroxyl groups present in the amino components need not be protected during the acylation. Furthermore, racemization of the peptide synthesized by this method is not observed as tested by the Anderson method.

The physical properties of the synthetic protected peptides prepared by this method are in agreement with those prepared by others methods, and consequently the present method may find a general use for activating the carboxyl group of an amino acid and for peptide synthesis. Use of our TTT

method for synthesis of some active oligopeptide is now in progress and will be reported in a subsequent paper. It should be mentioned in this connection that two papers related to acyl tetrahydrothiazole were published and made available to us only very recently.[6] This heterocyclic system has versatile reactivities and is worthy of further studies as a synthetic reagent.

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