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Zorc, Branka; Karlović, G.; Butula, Ivan

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Reactions with N-(1-benzotriazolylcarbonyl)-amino acids.
IV. The use of N-(1-benzotriazolylcarbonyl)-amino acid derivatives
in peptide synthesis

B. Zorc, G. Karlović* and I. Butula

Faculty of Pharmacy and Biochemistry, University of Zagreb, Croatia, Yugoslavia

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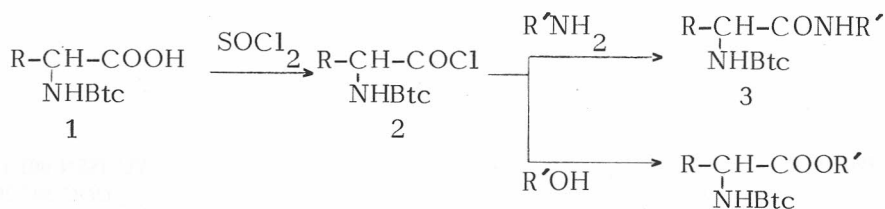
The use of the 1-benzotriazolylcarbonyl-(Btc)-group as an *N*-protecting and *N*-activating group in the synthesis of peptides was investigated. Removal of the Btc group from *N*-Btc-amino acids, their esters and amides under acidic conditions is possible, but has no advantages over removal of benzyloxycarbonyl-(*Z*)-group. *N*-Btc-amino acid esters react with *Z*-amino acids or *Z*-dipeptides yielding *Z*-dipeptide and *Z*-tripeptide esters, respectively. This process is accompanied with separation of benzotriazole and CO₂. Advantages and disadvantages of this method of peptide bond formation are discussed.

N-(1-Benzotriazolylcarbonyl)-(Btc)-amino acids¹ (**1**) have been previously used in peptide synthesis². The peptide bond formation was achieved by means of 1-benzotriazolylcarbonyl group as both by a *N*-protecting and C-activating group. In this paper we report new methods of peptide bond formation using the Btc group, either as a *N*-protecting or *N*-activating group.

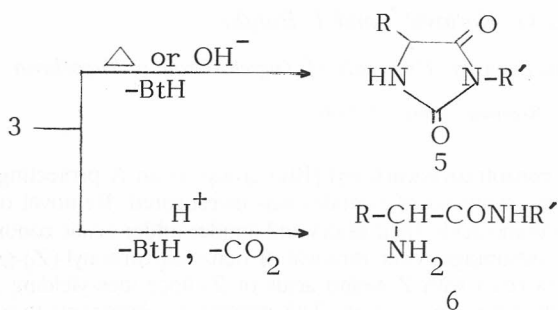
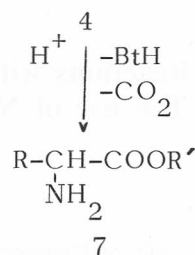
The Btc Group as an N-Protecting Group in the Peptide Bond Formation

The synthesis of *N*-(Btc)-amino acid amides (**3**) from **1** and their alkaline hydrolysis to hydantoins as the only products has already been reported³. *N*-Btc-amino acids (**1**), amides **3** and the here described *N*-Btc-amino acid esters **4** are quite stable in diluted hydrochloric acid. Acidic hydrolysis of the Btc group is observed after a longer treatment (several hours at room temperature). The degree of hydrolysis is higher at increased temperatures, but heating also enhances formation of hydantoins, e.g. Btc-*D,L*-phenylglycine benzyl amide (**3d**) in acetone/5% HCl (5 hrs, 60°C) gives *D,L*-phenylglycine benzyl amide (**6d**) and 3-benzyl-5-phenyl-hydantoin (**5a**) in 1:1 ratio. When the *N*-Btc-*D,L*-phenylglycine butyl amide (**3b**) is refluxed in xylene for 8 hrs, it cycles to 3-butyl-5-phenylhydantoin (**5b**) (60% yield). This reaction is in agreement with the known dissociation of carbamoyl benzotriazole to benzotriazole and isocyanates⁴ and their cyclization to hydantoins⁵:

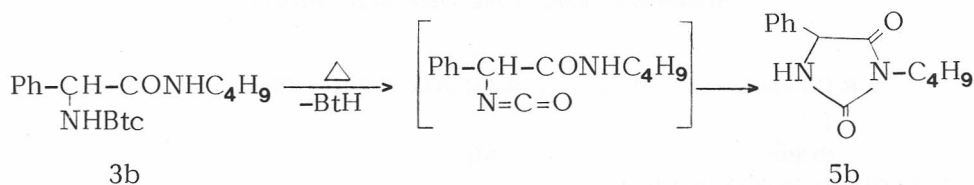
* Pliva Research Institute, Yu-41000 Zagreb, Croatia, Yugoslavia



BtH = benzotriazole



R	R'	compound			
		1	3 and 6	4	5
p-OH-C ₆ H ₅ CH ₂	-	a			
CH ₃	c-C ₆ H ₁₁		a		
C ₆ H ₅	C ₄ H ₉		b		b
C ₆ H ₅	c-C ₆ H ₁₁		c		
C ₆ H ₅	C ₆ H ₅ CH ₂		d		a
C ₆ H ₅ CH ₂	C ₆ H ₅ CH ₂		e		
C ₆ H ₅ CH ₂	CH ₃ SCH ₂ CH ₂ CH- CH ₂ OH		f		
H	CH ₃			a	
H	C ₆ H ₅ CH ₂			b	
CH ₃ SCH ₂ CH ₂	C ₂ H ₅			c	
C ₆ H ₅ CH ₂	CH ₃			d	
C ₆ H ₅ CH ₂	C ₆ H ₅ CH ₂			e	c
C ₆ H ₅	CH ₃			f	
CH ₃	C ₆ H ₅ CH ₂			g	
(CH ₃) ₂ CHCH ₂	C ₆ H ₅ CH ₂			h	



Acidolysis of Btc group is easier in trifluoroacetic acid (TFA): *N*-Btc-amino acid amides **3e**, **3f** and *N*-Btc-L-tyrosine (**1a**), after standing in TFA at room temperature for 24 hrs, produce amino acid amides **6e** and **6f**, and tyrosine, respectively. Table I shows the results of acidolysis of some *N*-Btc-amino acid derivatives.

Catalytic hydrogenation, which is a well known deblocking method for *Z*-protective group, proved to be unsuccessful in the case of Btc group: no hydrogen uptake occurred when *N*-Btc-amino acid amides were hydrogenated on Pd(5%)/C, Pd(5%)/BaSO₄ in ethanol or ethyl acetate.

The general conclusion is that the *N*-Btc group, as an *N*-protecting group, has no advantages over benzyloxycarbonyl-(*Z*)- and other alkyloxycarbonyl groups.

The Btc Group as an N-Activating Group in the Peptide Bond Formation

It was previously confirmed that 1-benzotriazole carboxylic acid amides (BtcNHR, "active ureas"), like some other, by Staab⁶ investigated carbamoylazoles, dissociate into benzotriazole and isocyanates⁴. It is also known that *N*-1-(imidazolylcarbonyl) and *N*-[1-(1,2,4-triazolyl)-carbonyl]-amino acid esters **a** at higher temperature dissociate into α -isocyanate esters **b** and the correspondingazole. Thus formed α -isocyanate esters react with *N*-protected amino acids (e.g. *Z*-amino acids) forming *N*-protected dipeptide esters **c**.

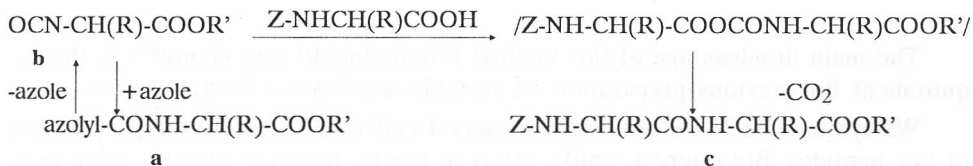
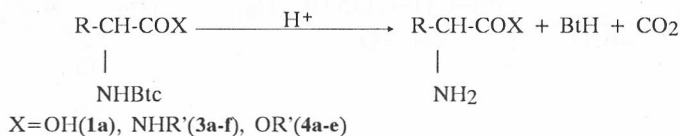


TABLE I
Acidolysis of some N-Btc-amino acid derivatives

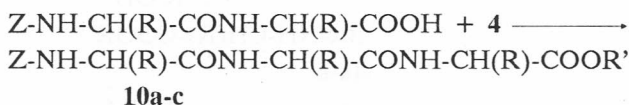
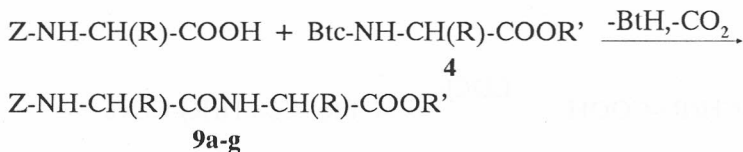


Compound	Reaction conditions			Product*
	Acid	Temp. (°C)	React. time (h)	
1a Btc- <i>L</i> -Tyr-OH	TFA	20	24.0	H- <i>L</i> -Tyr-OH
3a Btc- <i>D,L</i> -Ala-NHc-C ₆ H ₁₁	acetone/HCl	60	10.5	H- <i>D,L</i> -Ala-NHc-C ₆ H ₁₁ (6a)
3b Btc- <i>D,L</i> -Pgly-NHC ₄ H ₉	"	"	3.5	H- <i>D,L</i> -Pgly-NHC ₄ H ₉ (6b)
3c Btc- <i>D,L</i> -Pgly-NHc-C ₆ H ₁₁	"	"	21.0	H- <i>D,L</i> -Pgly-NHc-C ₆ H ₁₁ (6c)
3d Btc- <i>D,L</i> -Pgly-NHCH ₂ -C ₆ H ₅	"	"	5.0	H- <i>D,L</i> -Pgly-NHCH ₂ -C ₆ H ₅ (6d) + hydantoin (5a)
3e Btc- <i>L</i> -Phe-NHCH ₂ -C ₆ H ₅	"	"	3.2	H- <i>L</i> -Phe-NHCH ₂ -C ₆ H ₅ (6e) + hydantoin (5c)
3e "	TFA	20	24.0	H- <i>L</i> -Phe-NHCH ₂ -C ₆ H ₅ (6e)
3f Btc- <i>L</i> -Phe- <i>L</i> -methioninol	"	"	"	H- <i>L</i> -Phe- <i>L</i> -methioninol (6f)
4a Btc-Gly-OCH ₃	dioxane/HCl	100	2.0	H-Gly-OCH ₃ + H-Gly-OH
" "	TFA	72	0.66	" "
4b Btc-Gly-OCH ₂ -C ₆ H ₅	acetone/HCl	60	16.0	H-Gly-OCH ₂ -C ₆ H ₅ +H-Gly-OH
" "	dioxane/HCl	100	8.0	" "
" "	TFA	20	120.0	" "
" "	"	72	0.5	" "
4d Btc- <i>L</i> -Phe-OCH ₃	dioxane/HCl	100	1.25	H- <i>L</i> -Phe-OCH ₃ +H- <i>L</i> -Phe-OH
4e Btc- <i>L</i> -Phe-OCH ₂ -C ₆ H ₅	"	"	2.0	" "

* Hydantoin was not always isolated. For spot detection on TLC, a mixture of H₂SO₄ and MeOH (1:9)/120°C was used.

The main disadvantage of this method (Goldschmidt⁷ and Gante^{8,9}) is the requirement for previous preparation of unstable and toxic α -isocyanate esters.

We synthesized N-Btc-amino acid esters **4** and used them for the preparation of low peptides. Btc esters **4**, unlike esters **a**, can be prepared directly, since benzotriazole is an azole able to form azolylicarbonyl chloride⁴. N-Btc-amino acid esters **4** were synthesized in two ways:



The best results were obtained by heating the reactants for several hours in waterless xylene at 140°C. For isolation and purification of products **9** and **10**, recrystallization and column chromatography were used.

Reaction times, yields and the properties of the N-Z-di- and tripeptide esters are summarized in Table III.

The described method of peptide bond formation is a modification of the isocyanate method. This method offers some advantages: the N-Btc- amino acid esters may be considered as stable and non-volatile isocyanates and are, therefore, easier and less dangerous to handle than the α -isocyanate esters. This approach is particularly convenient in the synthesis of homologous compounds. Our method has no advantages over the other known methods of peptide bond formation.^{11,12}

EXPERIMENTAL

All melting points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 457 spectrophotometer. Specific rotation data were taken on the "Opton" polarimeter. For thin-layer chromatography, silica gel sheets Kieselgel 60 F₂₅₄ "Merck" were used. Solvent systems were benzene/ethylacetate 9:1, 7:3 or 1:1 and chloroform/methanol 9:1. For spot detection ninhydrin, iodine or a mixture of methanol and conc. sulfuric acid 9:1 were used. Column chromatography was performed on silica gel 0.063-0.200 mm. The N-Btc-amino acids, their chlorides,^{1,3} H-Gly-OBzl,²³ H-L-Met-OEt,²⁴ H-D-Pgly-OMe²⁵ and H-L-Phe-OBzl²⁶ were synthesized according to the literature. Z-L-Phe-OH, Z-Gly-L-Phe-OH and Z-L-Leu-L-Ala-OH were purchased from "Fluka". Z-L-Tyr(Bzl)-Gly-OH was prepared by saponification of the methyl ester following the method of Wünsch.²⁷

D,L-Alanine Cyclohexylamide (H-D,L-Ala-NH-c-C₆H₁₁) (6a)

A suspension of 2.21 g (7 mmol) of Btc-D,L-Ala-NH-c-C₆H₁₁ (**3a**) in 30 ml acetone and 30 ml 5% HCl was refluxed for 10.5 hrs. Acetone was removed in vacuo and the water solution was extracted several times with chloroform (until all of benzotriazole was removed). The aqueous layer was evaporated in vacuo. The crude product **6a** hydrochloride (1.45 g, 100%) was recrystallized from methanol/ether. m.p. 239-241°C (Lit.²⁸ 238-240°C).

IR(KBr): ν_{max} 3500-2500, 3280, 1675, 1545 cm⁻¹.

D,L-Phenylglycine Butylamide (H-D,L-Pgly-NHC₄H₉) (6b)

From 2.11 g (6 mmol) Btc-D,L-Pgly-NHC₄H₉ (**3b**) 0.92 g (63%) **6b** HCl was prepared (an analogous procedure to that for **6a**). m.p. of hydrochloride 64-65°C.

IR(KBr): ν_{max} 3660-2400, 1665, 1555, 1475 cm⁻¹.

C ₁₂ H ₁₉ ClN ₂ O (242.75)	<i>calc.</i>	C 59.37	H 7.88	N 11.54
	<i>found</i>	59.35	8.09	11.72

TABLE II
N-(1-benzotriazolylcarbonyl)-amino acid esters (4a-h)

REACTANTS		METHOD	SOLVENT	REACTION TIME / h	PRODUCT	YIELD / %	m. p. (°C)	SOLVENT FOR RECRYST.	IR (KBr or film) (cm ⁻¹)
Gly-OMe·HCl	BtcCl+NMM	B	benzene	72	Btc-Gly-OMe (4a)	85	133-134	acetone/ water	3370, 1745, 1530
Btc-Gly-Cl	BzIOH+TEA	A	benzene	1	Btc-Gly-OBzl (4b)	52	150-151	acetone, methanol	3360, 1755, 1730, 1530
Gly-OBzl·HCl	BtcCl+NMM	B	dioxane	1		46			
<i>L</i> -Met-OEt·HCl	BtcCl+NMM	B	dioxane	1.5	Btc- <i>L</i> -Met-OEt (4c)	81	oil	-	3350, 1740, 1520
Btc- <i>L</i> -Phe-Cl	MeOH	A	methanol	0.75	Btc- <i>L</i> -Phe-OMe (4d)	99	oil	-	3370, 1725, 1500
<i>L</i> -Phe-OMe·HCl	BtcCl+NMM	B	dioxane	2		77			
Btc- <i>L</i> -Phe-Cl	BzIOH+TEA	A	benzene	0.75	Btc- <i>L</i> -Phe-OBzl (4e)	64	oil	-	3400, 1740, 1515
<i>L</i> -Phe-OBzl·HCl	BtcCl+NMM	B	dioxane	1.5		82			
Btc- <i>D</i> -Pgly-Cl	MeOH	A	methanol	0.5	Btc- <i>L</i> -Pgly-OMe (4f)	94	72-75	benzene/ petrol- ether	3410, 1740, 1500
<i>D</i> -Pgly-OMe·HCl	BtcCl+NMM	B	dioxane	2		87			
<i>D</i> -Pgly-OMe·HCl	BtcCl+DEG	B	dioxane	2		80			
Btc- <i>D,L</i> -Ala-Cl	BzIOH+TEA	A	benzene	0.25	Btc- <i>D,L</i> -Ala-OBzl (4g)	72	70-71	ether/ petrol- ether	3340, 1755, 1730, 1525
Btc- <i>L</i> -Leu-Cl	BzIOH+TEA	A	benzene	0.75	Btc- <i>L</i> -Leu-OBzl (4h)	75	62-64	methanol	3320, 1725, 1505

TABLE III
Z-dipeptide- (9a-g) and *Z*-tripeptide esters (10a-c)

COMPOUND	REACT. TIME (h)	YIELD (%)	m. p. (°C)	Lit. m. p. (°C)	SOLVENT FOR RECRYST.	$[\alpha]_D^{20}$	Lit. $[\alpha]_D^{24}$	IR (KBr) (cm ⁻¹)
<i>Z</i> -Gly-Gly-OMe (9a)	6.5	60	63-65	63-65 ¹³ 66.5-67.5 ¹⁴	ethyl acetate/ petrolether	-	-	3320, 1740, 1690, 1660, 1530
<i>Z</i> -Gly-Gly-OBzl (9b)	7.0	55	110-112	110 ¹⁵ 111-112 ^{16,17}	methanol/ water	-	-	3380, 1740, 1710, 1655, 1530
<i>Z</i> -L-Phe-Gly-OBzl (9c)	4.5	75	133-134	130-131 ¹⁷ 135.5-137.5 ¹⁸ 138 ¹³	ethyl acetate/ petrolether	* -10.7° (c 0.1, AcOH)	* -9.2° (c 2, AcOH) ¹⁸	3300, 1740, 1695, 1660, 1540
<i>Z</i> -L-Tyr(Bzl)-Gly-OMe (9d)	10.0	66	127-128	126-127 ¹⁹	ethyl acetate	* -24.6° (c 0.76, DMF)	-23.1° (c 0.96, DMF) ¹⁹	3300, 1750, 1695, 1655, 1540
<i>Z</i> -L-Phe-L-Met-OEt (9e)	4.5	51	121-124	-	ethyl acetate/ petrolether	+11.7° (c 0.5, CHCl ₃)	-	3300, 1725, 1690, 1660, 1530
<i>Z</i> -Gly-L-Phe-OBzl (9f)	13.0	68	68-69	74 ²⁰	-	-4.8° (c 1, EtOH)	** -4.5° (c 1, EtOH) ²⁰	3390, 3320, 1730, 1705, 1655, 1530
<i>Z</i> -L-Phe-L-Phe-OBzl (9g)	8.5	75	152-153	149-150 ²¹ 156-157 ²⁰	methanol	+10.8° (c 2, CHCl ₃)	+9.1° (c 2, CHCl ₃) ²⁰	3300, 1735, 1700, 1655, 1550
<i>Z</i> -L-Tyr(Bzl)-Gly-Gly-OMe (10a)	12.0	65	152-155	161-163 ²²	ethyl acetate	** -15° (c 0.9, 50% THF)	** -18.8° (c 0.9, 50% THF) ²²	3400, 1740, 1715, 1675, 1500
<i>Z</i> -Gly-L-Phe-L-Met-OEt (10b)	12.0	53	98-100	-	ethyl acetate/ petrolether	-9.7° (c 0.89, EtOH)	-	3250, 1720, 1685, 1650, 1515
<i>Z</i> -L-Leu-L-Ala-D-Pgly-OMe (10c)	11.0	61	176-178	-	methanol/ water	** -82° (c 1, CHCl ₃)	-	3270, 1735, 1685, 1640, 1520

* *t* = 23°C ** *t* = 25°C

b) A solution of 0.50 g **3e** in 20 ml trifluoroacetic acid (TFA) was left at room temperature for 24 hrs. After removing TFA in vacuo, the residue was dissolved in ethyl acetate and extracted several times with 2% NaOH (in order to remove BtH). The organic layer was washed with water, dried over Na₂SO₄ and evaporated to give **6e** which was transformed into hydrochloride by means of HCl/2-propanol. Yield: 0.24 g (75%). IR spectrum, $[\alpha]_D^{20}$ and m.p. were identical to the product prepared following procedure a).

L-Phenylalanine-L-(1-hydroxymethyl-3-methylthiopropyl)amide (H-L-Phe-L-Methioninol) (6f)

A solution of 3.00 g (7 mmol) Btc-*L*-Phe-*L*-methioninol (**3f**) in 15 ml TFA was left at room temperature for 24 hrs. After removing TFA in vacuo, the residue was dissolved in water, acidulated with HCl (pH 2) and extracted 18 times with benzene. The aqueous layer was evaporated and the crude **6f** HCl was recrystallized from 2-propanol. Yield: 0.66 g (30%). IR spectrum, $[\alpha]_D^{20}$ and m.p. were identical to the test substance.²⁹ The mother liquor contained an additional amount of **6f** inured with benzotriazole.

3-Butyl-5-phenylhydantoin (5b)

0.30 g (0.85 mmol) Btc-*D,L*-Pgly-NHC₄H₉ (**3b**) was refluxed in 30 ml xylene for 8 hrs. After evaporating xylene under reduced pressure, the crude product **5b** was chromatographed (silica gel, chloroform/ethyl acetate 8:2). Yield: 0.12 g (60.5%) **5b**. m.p. 74-77°C (Lit.³ 72-76°C).

Acidolysis of Btc-amino Acid Esters

0.5 mmol of Btc-amino acid esters **4a-d** in 10 ml trifluoro acetic acid was reacted (for the reaction conditions see Table I) until no starting ester could be detected on TLC (silica gel sheets, benzene/ethyl acetate 1:1, chloroform/methanol 9:1, butanol/acetic acid/water 4:1:1). In most cases, during this period, acidolysis of ester group occurred parallel to acidolysis of Btc, so the products were both amino acid esters and free amino acids, respectively. The reaction products were not isolated, but were identified on TLC (silica gel sheets in benzene/ethyl acetate 1:1) (Figure 1.)

1. Btc-Gly-OMe
2. Btc-Gly-OBzl
3. Btc-*L*-Phe-OMe
4. Btc-*L*-Phe-OBzl
5. benzotriazole
6. H-Gly-OMe
7. H-Gly-OBzl
8. H-*L*-Phe-OMe
9. H-*L*-Phe-OBzl
10. H-Gly-OH
11. H-*L*-Phe-OH

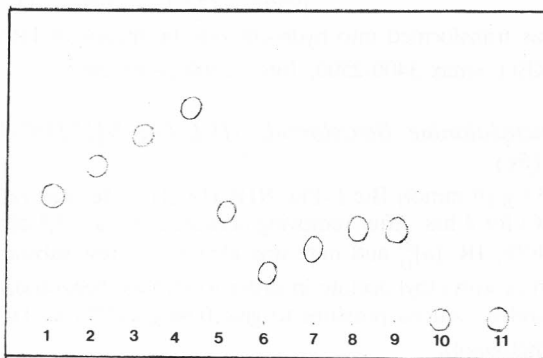


Figure 1. Acidolysis of Btc-amino acid esters: TLC of starting and final compounds

suspension, a solution of N-methyl-morpholine (NMM) (25 mmol) in 10 ml dioxane or benzene was added dropwise. The reaction mixture was stirred at room temperature (see Table II). N-Btc-amino acid esters were isolated as follows:

N-Btc-Glycine methyl ester (*Btc-Gly-OMe*) (**4a**): The reaction mixture was filtered and evaporated to dryness. The crude **4a** was recrystallized from acetone /water.

$C_{10}H_{10}N_4O_3$ (234.22)	calc. C 51.28 H 4.30 N 23.92
	found 50.99 4.58 23.82

N-Btc-Glycine benzyl ester (*Btc-Gly-OBzl*) (**4b**): The reaction mixture was filtered and evaporated to dryness. The residue was chromatographed on silica gel column (benzene/ethyl acetate 9:1).

N-Btc-L-Methionine ethyl ester (*Btc-L-Met-OEt*) (**4c**): The same isolation procedure as for **4b**. After **4c**, 7% of *N,N'*-carbonyl-bis(L-methionine ethyl ester) (**8a**) was eluated.

4c: $[\alpha]_D^{20} +8.9^\circ$ (c 12.3, $CHCl_3$).

$C_{14}H_{18}N_4O_3S$ (322.38)	calc. C 52.16 H 5.63 N 17.38
	found 52.39 5.63 17.56

8a: m.p. 87-89°C (Lit.³⁰ 91°C).

8d: IR(KBr): ν_{max} 3350, 1740, 1635, 1575 cm^{-1} .

N-Btc-L-Phenylalanine methyl ester (*Btc-L-Phe-OMe*) (**4d**): The same isolation procedure as for **4c**. 1.65 g (77%) **4d** and 0.18 g (14%) *N,N'*-carbonyl-bis(L-phenylalanine methyl ester) (**8b**) was eluated.

8b: m.p. 157-159°C. Lit.¹⁰ m.p. 159.5-160.5°C.

IR(KBr): ν_{max} 3300, 1735, 1650, 1500 cm^{-1} .

N-Btc-L-Phenylalanine benzyl ester (*Btc-L-Phe-OBzl*) (**4e**): The same isolation procedure as for **4b**.

N-Btc-D-Phenylglycine methyl ester (*Btc-D-Pgly-OMe*) (**4f**): The reaction mixture was filtered and evaporated to dryness. The residue was chromatographed on a silica gel column (benzene/ethyl acetate 8:2). Yield: 87% **4f** and 6% of *N,N'*-carbonyl-bis(D-phenylglycine methyl ester) (**8c**).

8c: m.p. 189-191°C. Lit.³⁰ m.p. 185-186°C.

IR(KBr): ν_{max} 3360, 1740, 1645, 1565 cm^{-1}

When the NMM was replaced with *N,N*-diethylglycine ethyl ester (DEG) as HCl acceptor 80% **4f** and 6% **8c** were isolated.

N-Z-Dipeptide (**9a-g**) and *N*-Z-tripeptide esters (**10a-c**): *General procedure*: A solution of N-Btc-amino acid ester (4 mmol) and N-Z-amino acid or N-Z-dipeptide (4 mmol) in 40 ml of waterless xylene was refluxed for 3-13 hrs (see Table III). The solvent was removed in vacuo. N-Z-di- or tripeptiden esters were isolated as follows:

N-Z-Glycyl-glycine methyl ester (*Z-Gly-Gly-OMe*) (**9a**): Unreacted Btc-Gly-OMe and BtH were separated from the mixture on a silica gel column using benzene/ethyl acetate 1:1 as eluent. Compound **9a** was eluated with methanol and recrystallized from ethyl acetate/petroleum ether.

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SAŽETAK

Reakcije s *N*-(1-benzotriazolilkarbonil)-aminokiselinama.IV. Upotreba derivata *N*-(1-benzotriazolilkarbonil)-aminokiselina u sintezi peptida

B. Zorc, G. Karlović i I. Butula

Ispitana je mogućnost primjene 1-benzotriazolilkarbonilne (Btc) skupine kao zaštitne, odnosno aktivirajuće skupine u sintezi peptida. Nekoliko primjera acidolize amida i estera *N*-Btc-aminokiselina pokazuje da je otcjepljenje *N*-zaštitne Btc-skupine u principu moguće. Sintetizirani su esteri *N*-Btc-aminokiselina, koji u reakciji s benziloksikarbonil-(*Z*)-aminokiselinama, odnosno *Z*-dipeptidima daju, uz otcjepljenje benzotriazola i CO₂, odgovarajuće terminalno zaštićene di- i tripeptide. Diskutira se o nedostacima i prednostima ovih reakcija.