

REACTION OF 4-BROMOALKYL-4-METHOXY-2,5-OXAZOLIDIONE WITH ALCOHOL
OR α -AMINO ACID ESTER AND TRANSFORMATIONS OF THE PRODUCTS

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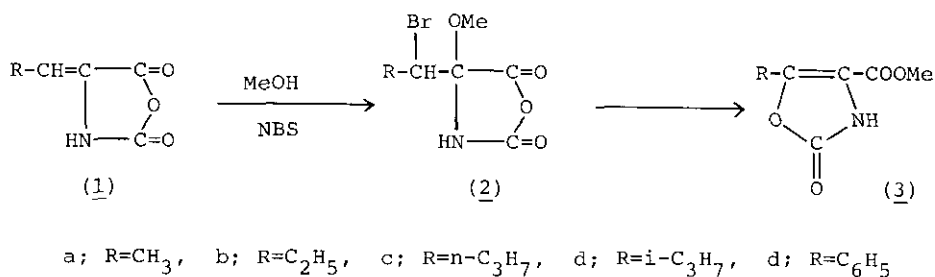
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Abstract—Reaction of N-carboxy α -dehydroamino acid anhydride with methanol in the presence of NBS gave 4-bromoalkyl-4-methoxy-2,5-oxazolidione, which was further treated with alcohol or α -amino acid ester to give extremely different two types of products, 2-oxazolinone and α -(oximino)acyl- α -amino acid derivatives respectively.

In a previous paper, we reported briefly that the reaction of N-carboxy α -dehydroamino acid anhydride (Δ NCA; 1)¹ with methanol in the presence of N-bromosuccinimide (NBS) gave the versatile methyl 5-alkyl-2-oxazolinone-4-carboxylate (3) via 4-bromoalkyl-4-methoxy-2,5-oxazolidione (2) by two steps.² Furthermore, the saturated NCA (2) reacted readily with other alcohol or even α -amino acid ester to give 3 and the unexpected α -(oximino)acyl- α -amino acid ester (5) respectively in one-pot,³ whereas the similar reaction of the unsaturated NCA (1) with alcohol or α -amino acid ester was carried out to give the corresponding α -dehydroamino acid and its dehydrodipeptide ester respectively.⁴⁻⁶

In the present paper, we wish to report in detail on the unusual and interesting behavior of 1 by the reaction with methanol in the presence of NBS and the transformation mechanisms of the very different two types of products. According to the procedure reported previously,² which was modified a little here, treatment of 1 (2 mmol) with methanol (40 ml) in the presence of NBS (2 mmol) under cooling for 40 minutes yielded 2, which was subsequently in situ

treated with an appropriate organic or inorganic base (2 mmol), such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and NaOH, at room temperature for 5 h. The concentration of the reaction solution thus obtained gave a crude residue, which was then purified on a silica gel column using a mixture of benzene and ethyl acetate (3 : 1 v/v) as the eluent to give 3 as colorless needles from ethyl acetate. As was reported,² the compound 2 is able to isolate purely as well in a quantitative yield.



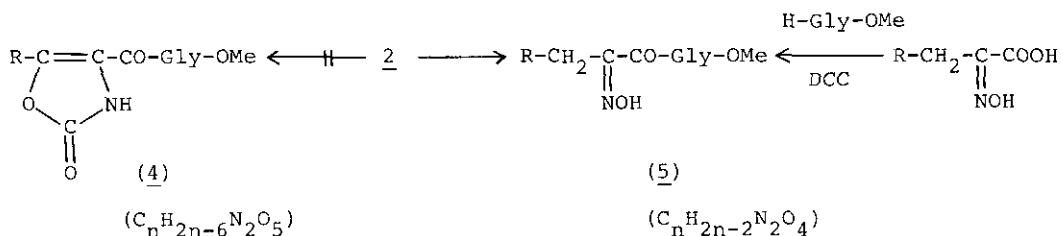
Scheme 1

Table 1. Yield of oxazolinone (3) from 1

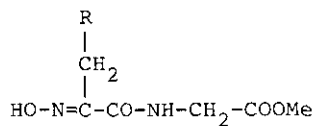
Compound No.	Yield (%)
<u>3a</u>	71
<u>3b</u>	64
<u>3c</u>	65
<u>3d</u>	61
<u>3e</u>	76

On the other hand, in order to obtain 5-alkyl-2-oxazolinone-4-carboxylglycine methyl ester (4), as in the case of the reaction of 1 with α -amino acid ester,⁶ the treatment of an equimolar 2 (20 mmol) with glycine methyl ester in THF (50 ml) in the presence of DBU (60 mmol) was performed at 0 °C for 7 h to give reaction mixture containing DBU salt. After removal of the solvent, to the

resulting residue was added ethyl acetate (200 ml) and then the salt was filtered off. The filtrate was washed successive with 1 M HCl and water once and then the organic layer was dried over anhydrous Na_2SO_4 . Evaporation of the solvent



Scheme 2

 Table 2. α -(Oximino)acylglycine methyl esters


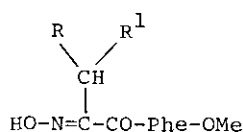
Compound		Yield (%)	$\text{mp } ^\circ\text{C}$	IR (KBr) cm^{-1}				$^1\text{H-NMR}$ (δ , CDCl_3)			
R				NH	COO	NHCO	C=N	-OH	-CONH-	$-\text{CH}_2-$	$\text{R}-\text{CH}_2-$
CH_3	65	124-125 ^a	3350	1770	1680 1550	1650	9.78 bs	8.93 bt	4.10 d (5.5)	2.40 q (7.5)	
C_2H_5	60	131-132 ^a	3300	1750	1680 1550	1655	9.94 bs	8.92 bt	4.06 d (6.0)	2.32 t (7.5)	
$n\text{-C}_3\text{H}_7$	45	126-127 ^a	3300	1750	1680 1550	1650	9.98 bs	8.90 bt	4.04 d (6.0)	2.32 q (8.0)	
$i\text{-C}_3\text{H}_7$	45	120-121 ^a	3340	1760	1690 1560	1650	9.78 bs	8.90 bt	4.05 d (5.5)	2.18 m	
C_6H_5	65	150-151 ^b	3320	1740	1680 1560	1650	9.68 bs	8.82 bt	4.06 d (6.0)	3.64 s	

^a Colorless needles from cyclohexane.

^b Colorless needles from CCl_4 .

gave a crude solid substance, which was purified on a silica gel column using a mixture of benzene and ethyl acetate (5 : 1 v/v) as the eluent. The fraction obtained was finally concentrated under reduced pressure to give colorless crystals, whose molecular formula was found to be in complete accord with $C_nH_{2n-2}N_2O_4$ in ca 56% yield, not to be the expected $C_nH_{2n-6}N_2O_5$. Based on the spectroscopic data, as is listed in Table 2, satisfactory elemental analysis, and the independent preparation from α -oximinocarboxylic acid and glycine methyl ester by the dicyclohexylcarbodiimide (DCC) method, the compound obtained above could be determined unambiguously to be α -(oximino)acylglycine methyl ester (5). Furthermore, the similar reaction of 2 with an appropriate

Table 3. α -(Oximino)acylphenylalanine methyl esters

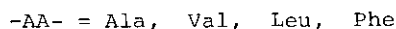
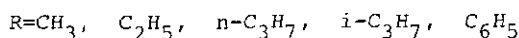
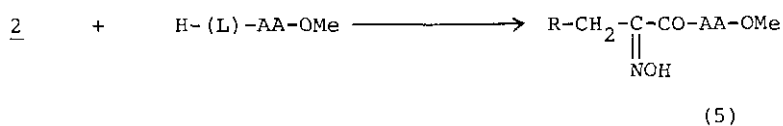


Compound		Yield (%) A ^a (B ^b)	mp °C ^c	IR (KBr) cm ⁻¹			¹ H-NMR (δ , CDCl ₃)			[α] _D ²⁰ (c, MeOH)
R	R ¹			NH (COO)	NHCO 1530	C=N 1630	-OH (J, Hz)	Ph-CH ₂ - (J, Hz)	R(R ¹)CH- (J, Hz)	
CH ₃	H	60 (43)	98-99	3300 (1750)	1660 1530	1630	10.14 bs	4.92 dt (6.0, 8.0)	2.60 q (7.5)	-1.1 ^o (1.12)
C ₂ H ₅	H	58 (40)	92-93	3375 (1745)	1660 1530	1630	9.17 bs	4.92 dt (6.0, 7.5)	2.59 t (7.5)	-10.0 ^o (1.00)
n-C ₃ H ₇	H	53 (35)	68-69	3380 (1745)	1660 1520	1630	8.50 bs	4.92 dt (6.5, 8.0)	2.60 t (7.5)	-1.3 ^o (0.98)
i-C ₃ H ₇	H	54 (37)	93-94	3300 (1750)	1660 1525	1630	9.24 bs	4.91 dt (6.5, 8.0)	2.55 d (7.5)	-1.5 ^o (1.18)
CH ₃	CH ₃	48 (23)	46-47	3300 (1750)	1660 1520	1630	9.02 bs	4.88 dt (6.5, 8.0)	3.44 m	-12.1 ^o (0.96)
C ₆ H ₅	H	51 (31)	112-113	3380 (1745)	1660	1630	9.40 bs	4.88 dt	3.95 s	5.4 ^o (1.01)

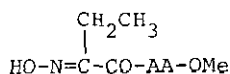
^a Yield from 2 and H-Phe-OMe. ^b Yield from α -oximinocarboxylic acid and H-Phe-OMe. ^c Colorless needles from ethyl acetate-hexane.

(L)- α -amino acid methyl ester [H-(L)-AA-OMe] was also achieved to give the several kinds of α -(oximino)acyl- α -(L)-amino acid methyl ester (5), as illustrated in Scheme 3.

The yields, melting points, and the physical constants of 5 are summarized in Tables 2, 3, and 4. As a result of comparison with the respective yield of 5 obtained from the two routes as shown in Tables 3 and 4, the synthesis of 5 by



Scheme 3

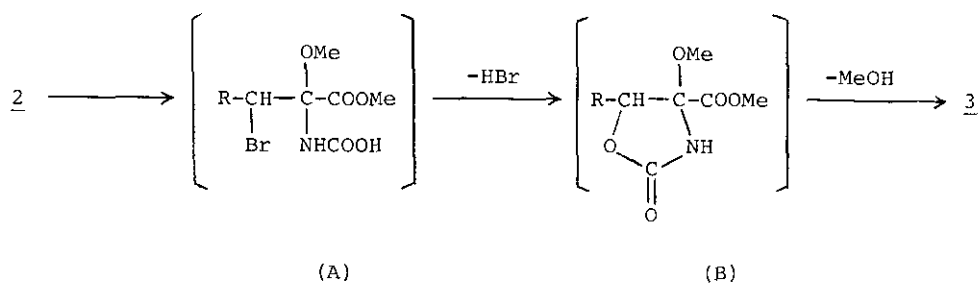
 Table 4. α -(Oximino)butanoyl- α -amino acid methyl esters


Compd.	Yield (%)	mp °C ^c	IR (KBr) cm ⁻¹				¹ H-NMR (δ , CDCl ₃)				[α] _D ²⁰ (c, MeOH)
			NH	COO	NHCO	C=N	-OH	-CONH-	CH ₃ CH ₂ -	R-CH ₂ -	
L-AA-	A (B ^b)						(J, Hz)				
Ala	50 (40)	89-90	3375	1740	1660 1525	1630	9.93 bs	7.46 d (7.0)	4.69 m	2.64 q (7.5)	6.6 ^o (1.01)
Val	58 (42)	syrup	3300	1740	1660 1520	1630	9.24 bs	7.40 d (7.5)	4.72 m	2.62 q (7.5)	9.3 ^o (1.01)
Leu	63 (47)	69-70	3350	1725	1660 1525	1630	9.68 bs	7.40 d (8.5)	4.69 dt (8.0, 8.5)	2.64 q (7.5)	-15.6 ^o (1.14)
Phe	60 (43)	98-99	3300	1750	1660 1530	1630	10.14 bs	7.00 -7.42 m	4.92 dt (6.0, 8.0)	2.60 q (8.0)	-1.1 ^o (1.12)

^a Yield from 2 and H-AA-OMe. ^b Yield from α -oximinocarboxylic acid and H-AA-OMe. ^c Colorless needles from ethyl acetate-hexane.

using 2 was found to be superior to that by the coupling of α -oximinocarboxylic acid by the DCC method.

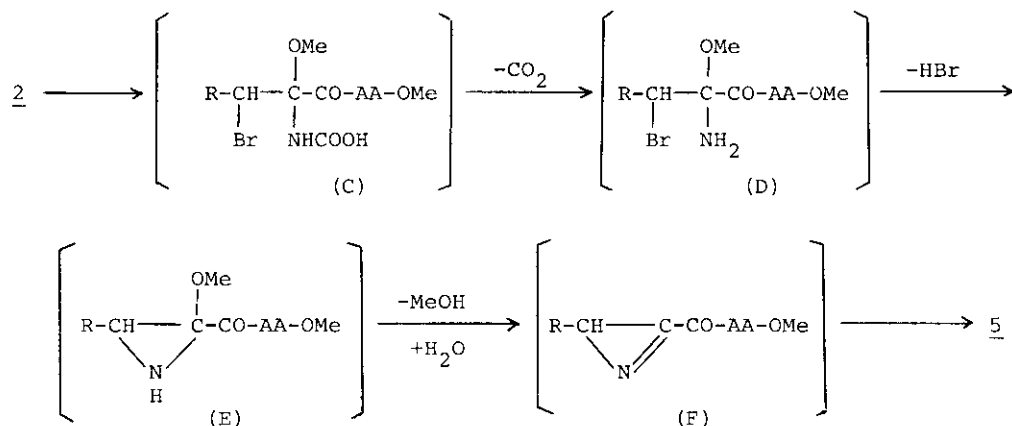
Judging from the structural types of 3 and 5, it was supposed that the two reactions between 2 and alcohol, and α -amino acid ester proceeded by the considerably different paths each other. Consequently, from the above results and facts, the transformation mechanisms of 2 to 3 was presumed that the oxazolidione ring opening and esterification took place simultaneously to form the corresponding α -(N-carboxyl)amino acid derivative (A) as an unstable intermediate, which was immediately cyclized between the vicinal bromo atom and N-carboxyl group at α -position, followed by the elimination of methanol from the resulting oxazolidinone derivative (B) to 3, as illustrated in Scheme 4.



Scheme 4

On the other hand, the conversion of 2 into 5 may be rationalized as follows. It was postulated that the ring cleavage and peptization of 2 was also carried out at the same time to yield (N-carboxyl)amino-dipeptide derivative (C), which was decarboxylated to give the corresponding N-deblocked dipeptide ester (D), instead of the formation of oxazolidinone derivative. Subsequently, the peptide ester thus formed was further dehydrobrominated to form the corresponding aziridine intermediate (E), followed by the elimination of methanol. The resulting azirine derivative (F) thus yielded was finally hydrolyzed to give 5, as illustrated in Scheme 5.

In addition, it is noteworthy that the compound 2 is available starting material for the synthesis of β -hydroxy- α -amino acid, α -hydroxyamino acid, and



Scheme 5

their unique peptides as well as 4,5-dialkyl- and 4,5-dihydroxy-2-oxazolidinone-4-carboxylates. The results will be reported and discussed elsewhere.

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