Tetrahedron Letters,Vol.24,No.41,pp 4451-4454,1983 0040-4039/83 $3.00 + .00
Printed in Great Britain

A Convenient Synthesis of Peptide Using Oxallates[1)]

Kazuyoshi Takeda, Izumi Sawada, Akira Suzuki, and
Haruo Ogura*

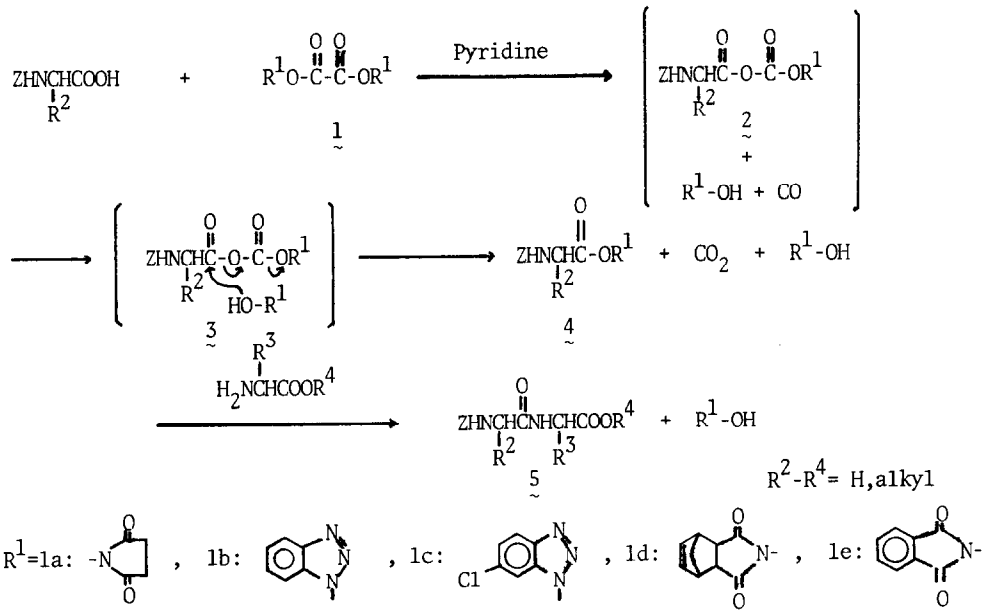
School of Pharmaceutical Sciences, Kitasato University
Shirokane, Minato-ku, Tokyo 108, Japan

The equimolar reactions of N-protected amino acids, amino acids or amino acid esters with oxallates (1a-1e) *having active ester groups in the presence of pyridine in acetonitrile afforded the corresponding dipeptides via active esters in good yields.*

The peptide synthesis reaction forming carboxamide is very important in peptide chemistry and many methods utilizing the reaction have been reported. Preparation method of active amino acid esters from N-hydroxyimides or 1-hydroxybenztriazole derivatives with dicyclohexylcarbodiimide (DCC) is widely used in peptide chemistry. However, DCC causes side reactions such as formation of acylisourea and Lossen rearrangement.[2)]

Recently, we have reported N,N'-disuccinimido carbonate (DSC)[3)] and N-succinimido diphenylphosphate (SDPP)[4)] as active esterification and peptide synthesis reagents without coupling reagent such as DCC. We now wish to report new reagents, oxallates (1a; N,N'-disuccinimido oxallate (DSO), 1b; 1,1'-dibenzotriazolo oxallate (DBTO), 1c; 1,1'-di(6-chrolobenzotriazolo) oxallate (Cl-DBTO), 1d; N,N'-dinorborneno oxallate (DNO), 1e; N,N'-diphthalimido oxallate (DPO)), which make the active esters and peptides more conveniently accessible. In this communication, we report a convenient method for the preparation of peptides by the equimolar reaction of N-protected amino acids and these esters with oxallates (1a-1e) containing active ester groups in the presence of pyridine in acetonitrile. The reaction will probably proceed as follows.

Intermadiate (2) is produced by a nucleophilic attack of carboxylate anion of N-protected amino acid on carbonyl group of oxallate (1) because the carbonyl group of oxallate (1) having electro attractive group such as active ester is easily displaced by the attack of nucleophile. The attack of the released alcohol on an intermadiate (3) forms the active ester (4) which is converted in turn into peptide.



Oxallates (1a-1e) were prepared from oxallyl chloride and N-hydroxy-imides or 1-hydroxybenztriazolo derivertives (0.1 mol) in an organic solvent such as dioxane, THF, acetone, acetonitrile or toluene. The solution was stirred under room temperature in the presence of pyridine (method A) or was refluxed in toluene (method B) to obtain oxallates in high yields as fine crystals.(Table II) Oxallates (1a-1e) are stable compounds and can be kept at room temperature over a long perid.

The typical procedure for preparing peptide is here with described; to a suspended acetonitrile (30 ml) solution of oxallate (1a; 1 mmol) was added a mixture of N-protected amino acid (1 mmol) and pyridine (1 mmol) in acetonitrile (10 ml). The reaction mixture became a clear solution after 0.5-3 hr. The reaction was continued for 3-5 hr. Further, aqueous solution of amino acid or amino acid ester hydrochloride (1 mmol) and NEt_3 (1 mmol) was added to the reaction mixture without isolation of active ester, and reaction mixture was treated in the general manner. Similarly, various dipeptides were prepared in good yields as summarized in the Table I.

In conclusion, the method using oxallates with active ester groups were more convenient than DCC method for active ester and peptide syntheses. These oxallates can be synthesized more conveniently and economically than DSC and SDPP.

Table I

Reagent	Product	Yield(%)	m.p. (°C)	m.p.(Ref.) (°C)	$[\alpha]_D$ (c,sol,°C)	$[\alpha]_D$(Ref.)
	Z-Phe-Gly-OEt	85.0	109-111	109-110[a]	-19.6 (1,EtOH,19)	-17.0[a]
DSO	Z-Val-Gly-OEt	64.0	165-167	162-164[a]	-28.0 (0.5,EtOH,22)	-27.0[a]
	Z-Ala-Ala-OH	100.0	149-151	153-155[b]	-20.8 (2,EtOH,20)	-25.4[b]
	Z-Phe-Gly-OEt	96.4	105-107	109-110[a]	-22.8 (1,EtOH,19)	-17.0[a]
DBTO	Z-Val-Gly-OEt	100.0	164-165	162-164[a]	-25.2 (1,EtOH,19)	-27.0[a]
	Z-Met-Met-OMe	93.3	94-96	98-100[c]	-29.4 (1,MeOH,19)	-25.6[c]
	Z-Phe-Gly-OEt	100.0	108-110	109-110[a]	-19.2 (1,EtOH,22)	-17.0[a]
Cl-DBTO	Z-Val-Gly-OEt	89.3	164-167	162-164[a]	-28.2 (1,EtOH,26)	-27.0[a]
	Z-Ala-Gly-OEt	90.0	99-101	99-101[d]	-23.8 (1,EtOH,18)	-22.1[d]
	Z-Phe-Gly-OEt	88.5	109-110	109-110[a]	-18.0 (1,EtOH,22)	-17.0[a]
DNO	Z-Val-Gly-OEt	83.3	165-166	162-164[a]	-25.0 (0.5,EtOH,23)	-27.0[a]
	Z-Ala-Gly-OEt	68.2	98-100	99-100[d]	-22.3 (1,EtOH,23)	-22.1[d]
	Z-Phe-Gly-OEt	93.8	108-110	109-110[a]	-17.2 (1,EtOH,23)	-17.0[a]
DPO	Z-Val-Gly-OEt	100.0	163-165	162-164[a]	-27.2 (0.5,EtOH,23)	-27.0[a]
	Z-Ala-Gly-OEt	94.5	97-99	99-100[d]	-25.2 (0.5,EtOH,23)	-22.1[d]

a: Ref.5; c=1, EtOH, 20°C. *b: Ref.3;* c=1.1, EtOH, 22°C.
c: Ref.6; c=0.7, MeOH, 19°C. *d: Ref.7;* c=3.08, EtOH, 20°C.

Table II

	m.p.(°C)	Yield(%) Method A	Yield(%) Method B	KBr IRν cm^{-1} -COCO-	Analysis(%) calcd (Found) C	H	N
DSO;	245-247(dec)	80.0	65.0	1720	42.26 (42.31	2.84 2.87	9.86 10.11)
DBTO;	159-160(dec)	95.0*	65.0	1725	51.86 (51.69	2.49 2.48	25.92 25.89)
Cl-DBTO;	not clear	90.0*	76.0	1720	42.77 (42.73	1.54 1.68	21.38 21.14)
DNO;	216-217	78.5	71.5	1720	58.26 (58.00	3.91 3.82	6.79 6.81)
DPO;	217-219(dec)	80.0	65.0	1720	56.85 (56.71	2.12 2.13	7.37 7.23)

* without pyridine

References

1) This constitutes Part IX. of a series entitled "Studies on Activating Methods of Functional Groups"
I) H. Ogura, K. Takeda, R. Tokue, T. Kobayashi, Synthesis, 394 (1978).
II) K. Takeda, T. Kobayashi, and H. Ogura, Chem. Pharm. Bull., 27, 536 (1979).
III) H. Ogura, T. Kobayashi, K. Shimizu, K. Kawabe, and K. Takeda, Tetrahedron Lett., 1979, 4745.
IV) H. Ogura, S. Nagai, and K. Takeda, Tetrahedron Lett., 21, 1967 (1980).
V) H. Ogura and K. Takeda, Heterocycles, 15, 467 (1981).
VI) H. Ogura and K. Takeda, Nippon Kagaku kaishi, 836 (1981).
VII) H. Ogura, O. Sato, and K. Takeda, Tetrahedron Lett., 22, 4817 (1981).
VIII) K. Takeda and H. Ogura, Synthetic Communications, 12, 213 (1982).
2) H. Gross, L. Bilk, Tetrahedron, 24, 6935 (1968).
3) 1), Part III.
4) 1), Part IV.
5) M. Miyoshi, Bull. Chem. Soc. Jpn., 46, 1489 (1973).
6) S. Terashima, M. Wagatsuma, and S. Yamada, Tetrahedron., 29, 1487 (1973).
7) M. Furukawa, N. Hokama, T. Okawara, Synthesis, 42, 1983.

(Received in Japan 27 June 1983)