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A NEW METHOD FOR THE SYNTHESIS OF PEPTIDES USING THE ADDUCTS OF PHOSPHORUS COMPOUNDS AND TETRAHALOMETHANES

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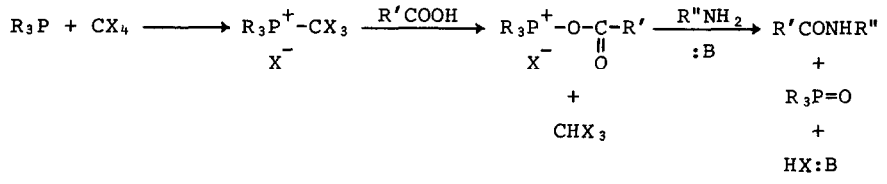
It has been known that the carboxylic acids are converted to the corresponding acid halides by treatment with the adduct of triphenylphosphine and carbon tetrachloride[1] or bromine.[2] Recently, Barstow and Hruby reported a simple method for the synthesis of amides using triphenylphosphine and bromotrichloromethane.[3] They also briefly tested the possibility of using this method for the synthesis of peptides. However, they neither examined the racemization test under fragment condensation nor synthesized di- or tripeptides except for Z-Phe-Gly-OEt.

Hruby's report prompted us to communicate our results. We had already investigated a new method for the synthesis of peptides using the adducts of phosphorus compounds (R_3P) and tetrahalomethanes (CX_4), and had found reaction conditions under which the risk of racemization appeared to be very small. Moreover, we had prepared several di- and tripeptides and examined the influence of these adducts on the side chain functions of amino acids.

Phosphines and phosphorous amides, e.g. $n\text{-}Bu_3P$, $(Me_2N)_3P$, $(Et_2N)_3P$, and $(Me\text{-}N\langle\rangle N)_3P$[4] were used as phosphorus compounds. These are very reactive because of their high basicity. Ph_3P and $(MeO)_3P$ were less satisfactory in producing peptides in high yield and with high optical purity. Carbon tetrachloride and carbon tetrabromide were used as tetrahalomethane. The former is better for this purpose since the excess of CX_4 and the reduced by-product (CHX_3) are easily removed. The assumed mechanism in this novel reaction is shown below.



The general procedure is as follows. CCl_4 or CBr_4 is added dropwise to a solution of N-protected amino acid or peptide (1 equiv), amino acid or peptide ester (1 equiv), phosphine or phosphorous amide (1 equiv), and base (2 equiv) in THF or DMF for 5 ∿ 30 min at -20∿0°. The mixture is allowed to stand overnight at room temperature. After water is poured into the solution, the product is extracted with AcOEt, then the organic layers are washed with 5% HCl, sat. $NaHCO_3$, and sat. NaCl and dried over $MgSO_4$. Evaporation of the solvent gives the peptide. In some cases, peptides are purified by column chromatography on silicic acid.

We examined the stringent Young racemization test[5] under several conditions and Bz-Leu-Gly-OEt was obtained in 60∿85% yields. Results are summarized in Table I.

Table I Young Racemization Test

Run	R_3P	CX_4	Base	Temp.	Solv.	Bz-Leu-Gly-OEt[6]		
						Mp	$[\alpha]_D^{20}$	L-Isomer(%)
1	Ph_3P	CCl_4	Me-N◯O	-15	THF	146∿149	-4.2	12.4
2	$(Me_2N)_3P$	CBr_4	Me-N◯O	-20	DMF	157∿159	-32.5	95.6
3	$(Et_2N)_3P$	CCl_4	$(Et_2N)_3P$	-15	THF	157∿158	-33.2	97.6
4	$n\text{-}Bu_3P$	CBr_4	Me-N◯O	-20	DMF	157∿159	-33.2	97.6
5	$n\text{-}Bu_3P$	CBr_4	H-Gly-OEt	0	DMF	155∿156	-31.1	91.5
6	(Me-N◯N)$_3$P	CCl_4	Me-N◯O	-20	THF	156∿158	-32.6	95.9
7	(Me-N◯N)$_3$P	CCl_4	(Me-N◯N)$_3$P	-15	THF	157∿158	-33.0	97.1

When phosphorous amides, i.e. $(Me_2N)_3P$, $(Et_2N)_3P$, and (Me-N◯N)$_3$P are used, oxidated phosphoric amides ($R_3P=O$) are easily removed by dilute aqueous

HCl and neutral peptide derivatives are generally obtained directly in a chromatographically pure state before recrystallization (see, Runs 2, 3, 6, and 7). In this new reaction, a by-product, HCl or HBr, is formed, but no "chloride ion effect"[7] is observed and amino acid or peptide ester hydrochloride can be also used as the starting material together with one more equiv of a base. Even the polar solvent DMF, in which racemization is thought to occur easily,[8] scarcely influences racemization. We ascribe this remarkable freedom from racemization even in a polar solvent to the low intrinsic reactivity of the resonance-stabilized acyloxyphosphonium intermediate.[9] This is especially useful in the synthesis of long peptides.

We also prepared several di- and tripeptides under the reaction conditions described above. All peptides were obtained in moderate yields and were identified by comparison of their mp, $[\alpha]_D$, and IR spectra with authentic samples or with values in the literature (Table II).

Table II Preparation of Peptides

Run	R_3P	CX_4	Base	Product	Mp	$[\alpha]_D$ (Temp.	c.	Solv.)
1	$(Et_2N)_3P$	CCl_4	$(Et_2N)_3P$	Z-Gly-Gly-OEt	82	———		
2	$(Me_2N)_3P$	CCl_4	$(Me_2N)_3P$	Z-Ala-Gly-OEt	97∿8	-24.0 (20	1.0	EtOH)
3	n-Bu_3P	CBr_4	Me-N◯O	Z-Phe-Leu-OMe	110∿1	-24.7 (20	3.1	MeOH)
4	(Me-N◯N)$_3$P	CCl_4	(Me-N◯N)$_3$P	Z-Phe-Gly-OEt	112	-16.7 (20	5.0	EtOH)
5	n-Bu_3P	CBr_4	Me-N◯O	Z-Ser-Gly-OEt	106∿7	-5.9 (20	1.0	EtOH)
6	(Me-N◯N)$_3$P	CCl_4	(Me-N◯N)$_3$P	Z-Ala-Val-OMe	84	-38.3 (20	1.0	MeOH)
7	$(Et_2N)_3P$	CCl_4	$(Et_2N)_3P$	Z-Ala-Phe-OMe	99	-14.2 (22	1.0	MeOH)
8	n-Bu_3P	CBr_4	Me-N◯O	Z-Thr-Phe-OMe	107∿8	+6.1 (22	1.0	AcOH)
9	(Me-N◯N)$_3$P	CCl_4	Me-N◯O	Z-Pro-Phe-OMe	73∿5	-37.3 (20	2.0	MeOH)
10	n-Bu_3P	CBr_4	Me-N◯O	Z-Met-Gly-OEt	96∿7	-18.6 (27	4.5	EtOH)
11	(Me-N◯N)$_3$P	CCl_4	Me-N◯O	Z-Glu(OEt)-Gly-OEt	97∿9	-15.8 (25	2.0	EtOH)
12	n-Bu_3P	CBr_4	Me-N◯O	Z-Asn-Gly-OEt	188∿9	-4.4 (20	1.0	DMF)
13	(Me-N◯N)$_3$P	CCl_4	Me-N◯O	Z-Ala-Phe|Met-OMe[10]	162∿3	-53.2 (20	1.0	MeOH)
14	(Me-N◯N)$_3$P	CBr_4	(Me-N◯N)$_3$P	Z-Leu-Leu|Val-OMe[10]	127∿9	-53.7 (20	1.0	MeOH)

No difficulties were observed when the side chains of methionine, serine, threonine, or asparagine were present without protection.

As the present method gives various peptides in good yields and with high optical purity using easily available reagents, we are now preparing some biologically active peptides by this new method.

REFERENCES AND FOOTNOTES

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3) L. E. Barstow and V. J. Hruby, J. Org. Chem., 36, 1305 (1971).

4) $(Me\text{-}N\bigcirc N)_3P$ was prepared by the reaction of PCl_3 with $Me\text{-}N\bigcirc NH$ according to the general method. It shows mp of 74°.

5) M. W. Williams and G. T. Young, J. Chem. Soc., 881 (1963).

6) Lit.[5] mp 156.5~157°, $[\alpha]_D^{20}$ -34.0°(c 3.1, EtOH).

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8) B. Liberek and A. Michalik, Roczniki Chem., 40, 781 (1966).

9) Cf. G. Gawne, G. W. Kenner, and R. C. Sheppard, J. Am. Chem. Soc., 91, 5669 (1969).

10) The vertical line indicates the point of coupling.