

A CONVENIENT METHOD FOR THE SYNTHESIS OF CARBOXAMIDES AND PEPTIDES  
BY THE USE OF TETRABUTYLAMMONIUM SALTS

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Various carboxamides and peptides are prepared in good yields by treatment of free acids and amines in H<sub>2</sub>O-dichloromethane or aqueous THF with bis(o-nitrophenyl) phenylphosphonate in the presence of tetrabutylammonium hydrogen sulfate or bromide. Carboxylic esters are also successfully converted to amides via carboxylate salts in one-pot.

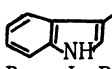
Recently, we have reported an efficient method for the synthesis of peptides using bis(o-, or p-nitrophenyl) phenylphosphonate as a coupling reagent.<sup>1)</sup> In the method, the tetrabutylammonium salt of N-protected amino acid or peptide is used as a carboxyl component, and the phosphonate liberated along with new peptide is converted to the corresponding ammonium salt. The other co-product is nitrophenol, therefore, the reaction requires no free base such as tertiary amine which often causes serious problems such as racemization during condensation.<sup>2)</sup> Employment of the quaternary ammonium salt also enables the reaction to proceed smoothly because of increased solubility and nucleophilicity of the carboxyl component, including peptides which are sparingly soluble in organic solvents. Preparation of the quaternary ammonium salts of acids in the method is carried out prior to the coupling reaction according to several methods.<sup>1)</sup> Although these procedures are not so tedious, formation of the salts in situ is synthetically more preferable. Based on this standpoint, our efforts have been focused on applying both phase transfer technique and ion pair extraction method to the synthesis of carboxamides using bis(o-nitrophenyl) phenylphosphonate(1) as a coupling reagent.

Method A consists of the reaction of both carboxyl and amino components with phosphonate 1 in the presence of 10 mol% of tetrabutylammonium hydrogen sulfate and inorganic bases (KOH and K<sub>2</sub>CO<sub>3</sub>). In Method B, Tetrabutylammonium bromide and Molecular sieve are employed in place of the sulfate and potassium carbonate used in Method A.<sup>3)</sup>

The followings are typical procedures for Method A and B. Method A: To a mixture of 4-phenylbutyric acid (0.45 mmol), potassium hydroxide (0.50 mmol), and tetrabutylammonium hydrogen sulfate (0.045 mmol) was added water (about 3.0 mmol) and the resulting slurry was stirred with dichloromethane (2 ml). After addition of dl-1-phenylethylamine (0.54 mmol) in dichloromethane (2 ml) and potassium carbonate (1.44 mmol), the mixture was stirred vigorously for about 30 min and

Table 1. Synthesis of carboxamides from free carboxylic acids.

$$R^1CO_2H + R^2R^3NH \xrightarrow[\text{KOH, } n\text{-Bu}_4\text{N}^+\text{X}^-]{\text{Ph-P(=O)(NO}_2\text{)(C}_6\text{H}_4\text{)}_2} R^1CONR^2R^3$$

Carboxamide <sup>a), b)</sup>	Method	Conditions <sup>c)</sup>	Yield(%)
Ph(CH <sub>2</sub> ) <sub>3</sub> CONHCH(Me)Ph	A	r.t., 4 h	quant.
CH <sub>3</sub> (CH <sub>2</sub> ) <sub>4</sub> CONHCH(Me)Ph	A	r.t., ON	89
α-Naph-CH <sub>2</sub> CONHCH(Me)Ph	A	r.t., ON	98
Me <sub>2</sub> CHCONHCH(Me)Ph	A	r.t., ON	95
Me <sub>3</sub> CCONHCH(Me)Ph	A	r.t., ON	90
(Me) <sub>2</sub> C=CHCONHCH(Me)Ph	A	r.t., 6 h	85
c-C <sub>3</sub> H <sub>5</sub> CONHCH(Me)Ph	A	r.t., ON	79
Ph(CH <sub>2</sub> ) <sub>3</sub> CONH(CH <sub>2</sub> ) <sub>7</sub> CH <sub>3</sub>	A	r.t., 4.5 h	88
Ph(CH <sub>2</sub> ) <sub>3</sub> CON(Me)CH <sub>2</sub> Ph	A	r.t., 4 h	95
PhCO(CH <sub>2</sub> ) <sub>2</sub> CONHCH(Me)Ph	A	r.t., ON	87
CH <sub>3</sub> (CH <sub>2</sub> ) <sub>10</sub> CONHCH <sub>2</sub> Ph	B	r.t., 5 h	98
CH <sub>3</sub> (CH <sub>2</sub> ) <sub>10</sub> CONMe <sub>2</sub> <sup>d)</sup>	B	r.t., ON	90
(Me) <sub>2</sub> C=CHCONHCH <sub>2</sub> Ph	B	r.t., 5 h	95
 CH <sub>2</sub> CONHCH <sub>2</sub> Ph	B	r.t., 3.5 h	82
Boc-L-Phe-Gly-OEt	B	r.t., ON	84
Z-Gly-L-Phe-OBzl <sup>e)</sup>	B	r.t., 24 h	95
Boc-Gly-L-Phe-OBzl <sup>e)</sup>	B	r.t., 2 h	88
Z-L-Phe-Gly-OEt	B	r.t., 1.5 h	93
Bz-L-Leu-Gly-OEt <sup>f)</sup>	B	-15 ~ -5°, 22 h	82

a) All compounds but peptides exhibited ir and nmr spectroscopic data in accordance with assigned structures. Peptides were characterized by comparing their  $[\alpha]_D$  and mp with literature values.

b) 1-Phenylethylamine used as an amino component is dl-form in all cases.

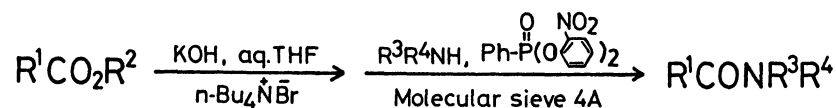
c) ON=overnight.


d) Hydrochloric acid salt of dimethylamine was used with equimolar amount of triethylamine.

e) p-Toluenesulfonic acid salt of L-Phe-OBzl was used with equimolar amount of triethylamine.

f) Young test result (94% optical purity).

Table 2. Transformation of carboxylic esters to carboxamides



Carboxylic ester	carboxamide <sup>a)</sup>	Conditions of coupling reaction <sup>b)</sup>	Yield(%)
PhCH <sub>2</sub> CO <sub>2</sub> Et	PhCH <sub>2</sub> CONHCH <sub>2</sub> Ph	r.t., 7 h	90
n-C <sub>17</sub> H <sub>35</sub> CO <sub>2</sub> Et	n-C <sub>17</sub> H <sub>35</sub> CONMe <sub>2</sub> <sup>c)</sup>	r.t., 2 h	78
PhCH <sub>2</sub> CO <sub>2</sub> Et	PhCH <sub>2</sub> CONMe <sub>2</sub> <sup>c)</sup>	r.t., 3 h	72
PhCH <sub>2</sub> CO <sub>2</sub> Et	PhCH <sub>2</sub> CON 	r.t., 2 h	86
Boc-L-Phe-Gly-OEt	Boc-L-Phe-Gly-Leu-OMe <sup>c)</sup>	0°C, 14 h then r.t., 5 h	79
Z-Gly-L-Phe-OBzl	Z-Gly-L-Phe-Gly-OEt <sup>c), d)</sup>	-10 ~ 0°C, 24 h	73

a) See footnote a in Table 1 for identification of each product.

b) Reaction time of saponification step is 6 h uniformly.

c) Amino component was used as its hydrochloric acid salt with equimolar amount of triethylamine.

d)  $[\alpha]_D^{27}$ -12.0(c 2, EtOH) [lit.,<sup>9)</sup>  $[\alpha]_D^{23}$ -12.4(c 2, EtOH)].

then bis(o-nitrophenyl) phenylphosphonate (0.54 mmol) and dichloromethane (2 ml) was added. After kept stirring for 4 h, ethyl acetate and water were added and the organic layer was washed successively with brine, 1 N NaOH solution, brine, 1 N HCl solution and brine, dried (Na<sub>2</sub>SO<sub>4</sub>), then evaporated. The residue was subjected to column chromatography on alumina (CHCl<sub>3</sub>/AcOEt 9/1) to afford N-(1-phenylethyl)-4-phenylbutyramide in quantitative yield, mp 82-83°C (from hexane-ethyl acetate).<sup>4)</sup> Method B: To a THF(2 ml) solution containing potassium hydroxide (0.5 mmol) and water (about 3.0 mmol) was added tetrabutylammonium bromide (0.45 mmol) and N-benzyloxycarbonyl-L-phenylalanine (0.45 mmol). The mixture was stirred with Molecular sieve 4 A (250-300 mg) for about 1 h. After addition of ethyl glycinate (0.5 mmol) in THF (1.0 ml) and the phosphonate (0.5 mmol), the resulting mixture was stirred for 1.5 h. The insoluble materials were filtered and washed with ethyl acetate. The filtrate was treated in the usual manner and Z-L-Phe-Gly-OEt was isolated in 93% yield,  $[\alpha]_D^{26}$ -16.8°(c 2, EtOH), mp 105.5-107°(from ethyl acetate-petroleum ether).<sup>5)</sup>

Various carboxamides and peptides were similarly synthesized in good yields as shown in Table 1.

In both methods, a limited amount of water was used for smooth formation of potassium salts of acids and the addition of water was found to promote the present reactions while complete removal of moisture is generally required in dehydrative condensation reactions. Potassium ion as a counter cation of carboxylate anion was more suitable with regard to yield than lithium or sodium ion. In Method A, addition of potassium carbonate gave the best result among various additives employed (Molecular sieve 4A, Na<sub>2</sub>SO<sub>4</sub>, MgSO<sub>4</sub>, neutral alumina,

Celite, and  $\text{KHCO}_3$ ). Employment of equimolar amount of tetrabutylammonium bromide in Method B gave better results than the use of a catalytic amount of the bromide.

The above procedure starts from conversion of free carboxylic acids to the potassium salts. The salts may be derived also by saponification of carboxylic esters before the coupling reaction in a same vessel. This route was readily realized by applying Method B. Thus, a carboxylic ester was treated first with slightly excess of potassium hydroxide (ca. 25% aqueous KOH solution) in THF (2.5 ml THF/1.0 mmol ester) in the presence of equimolar amount of tetrabutylammonium bromide and further procedure followed in the same vessel that described in Method B giving the corresponding carboxamide in good yield. The saponification step completes within 6 h and the results are listed in Table 2. Conversion of esters to the corresponding carboxamides is generally carried out by two separate reactions, that is, hydrolysis and amide bond formation especially in the case of peptide synthesis. However, the present method enables the one-pot synthesis of carboxamides and peptides from the corresponding esters.<sup>10)</sup>

#### References and Notes

- 1) T. Mukaiyama, N. Morito, and Y. Watanabe, *Chem. Lett.*, 1979, 1305.
- 2) Wakselman and Acher reported interesting results in their new method for the synthesis of peptides: M. Wakselman and F. Acher, *Tetrahedron Lett.*, 21, 2705 (1980).
- 3) The use of potassium carbonate or Molecular sieve effectively prevents hydrolysis of the coupling reagent.
- 4) Found: C, 81.11; H, 8.22; N, 5.08%. Calcd. for  $\text{C}_{18}\text{H}_{21}\text{NO}$ : C, 80.86; H, 7.91; N, 5.23%.
- 5) Literature values:  $[\alpha]_{\text{D}}^{20} -16.8^\circ$  (c 2, EtOH)<sup>6)</sup>;  $[\alpha]_{\text{D}}^{16} -19.2^\circ$  (c 4.1, EtOH);<sup>7)</sup>  $[\alpha]_{\text{D}}^{25} -16.0^\circ$  (c 2, EtOH).<sup>8)</sup> mp 110-2°C;<sup>6)</sup> 107.5-108.5°C;<sup>7)</sup> 109-110°C.<sup>8)</sup>
- 6) T. Mukaiyama, R. Matsueda, and M. Suzuki, *Tetrahedron Lett.*, 1970, 1901.
- 7) D. W. Clayton, J. A. Farrington, G. W. Kenner, and J. M. Turner, *J. Chem. Soc.*, 1957, 1398.
- 8) G. W. Anderson and R. W. Young, *J. Am. Chem. Soc.*, 74, 5307 (1952).
- 9) M. Goodman and K. C. Stueben, *J. Am. Chem. Soc.*, 81, 3980 (1959).
- 10) The method affords secondary carboxamides such as N,N-dimethylcarboxamides which are synthetic intermediates in transformation of esters to aldehydes using partial reduction: H. C. Brown and A. Tsukamoto, *J. Am. Chem. Soc.*, 86, 1089 (1964).

(Received November 22, 1980)