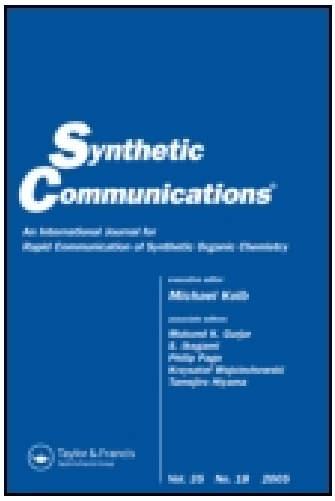

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AN EFFICIENT AMIDE-FORMING REACTION USING TRIBUTYLTRICHLOROMETHYLPHOSPHONIUM CHLORIDE

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AN EFFICIENT AMIDE-FORMING REACTION USING TRIBUTYLTRICHLORO-METHYLPHOSPHONIUM CHLORIDE

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ABSTRACT

An efficient and expeditious amide-forming reaction is described via a combination of tributylphosphine and carbon tetrachloride (*in situ* generation of tributyltrichloromethylphosphonium chloride) in the absence of *tertiary* amines.

A number of additives in peptide coupling reactions, such as HOBt (1), HOOBt (2), and HOAt, have been developed in order to enhance the reaction rate of peptide formation when used either in combination with a carbodiimide, or another coupling reagent in the presence of *tertiary* amines. HOAt incorporates both *tertiary* amine and HOBt elements within a single molecule. However, the DCC-HOAt promoted coupling in the presence of NMM requires usually several hours in the reaction time (3). Since racemization during coupling is a base-catalyzed process, it is judicious to develop conditions that exclude the *tertiary* amine from the reaction mixture. This communication discloses a practical amide-forming reaction using a combination of tributylphosphine and carbon tetrachloride in DMF in the absence of *tertiary* amines.

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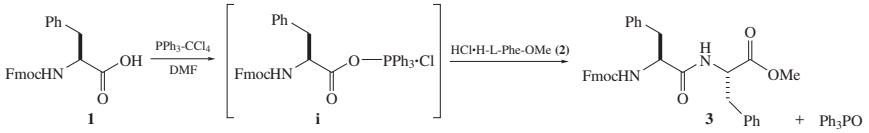
It was observed in our laboratory that the addition of base was not necessary in the coupling reaction of *N*-protected amino acid chlorides with C-blocked amino acid hydrochloride salts when using DMF as a solvent. The coupling reaction of *N*-protected amino acid chloride (synthesized from the corresponding amino acid *via* 1-chloro- *N,N,*2-trimethylpropenylamine (4)) and *C*-protected amino acid hydrochloride salt in DMF in the absence of *tertiary* amine afforded the corresponding peptide in good to excellent yield. Therefore, DMF can adequately dissociate the amine hydrochloride to the free amine and its acid and act as a buffer in the reaction. However, both preparation and application of amino acid chlorides remain fairly limited; the generation of acid chlorides *in situ* from the corresponding *N*-protected amino acids in the presence of an amino acid acceptor in DMF has not been successful. On the other hand, the ordinary carboxylic acids (non-amino acids) can be converted into the acid chlorides under neutral conditions by treatment with triphenylphosphine in carbon tetrachloride (5,6). *N*-methoxyamide synthesis using CBr_4-Ph_3P in CH_2Cl_2 in the presence of Et_3N was reported (6). When this transformations was applied to Fmoc-L-Phe-OH (**1**) in DMF, the rate limiting step for the formation of the acid chloride proved to be the attack of chloride anion onto the acyloxyphosphonium intermediate (**i**), which is stable under the conditions. No acid chloride formation was observed at room temperature. Nonetheless, this intermediate (**i**) was polarized enough to react with *C*-protected amino acid hydrochlorides. For example, the aminolysis of **i** with HCl·H-L-Phe-OMe (**2**) afforded dipeptide (**3**) in 55% yield together with triphenylphosphine oxide as a by-product (Scheme 1). More conveniently, the desired dideptide **3** was formed in 60 min by addition of Ph_3P into a mixture of **1**, **2** and CCl_4 in DMF.

In order to accelerate the reaction rate and facilitate separation from Ph_3PO, triphenylphosphine was replaced by tributylphosphine. The same coupling reaction of **1** and **2** with nBu_3P afforded **3** within 10 min in 75% yield without detectable racemization by ^{1}H-NMR. The abbreviations for amino acids follow the IUPAC-IUB Joint Commission on Biochemistry Nomenclature. The utility of this rapid and simple method for the formation of peptide bonds under mild conditions was verified and is summarized in Table 1. The rate difference between the conditions of Ph_3P-CCl_4 and nBu_3P-CCl_4 will be attributable not only to the reactivity of



Scheme 1.

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Table 1. The CCl_4-nBu_3P Promoted Dipeptide Formations*

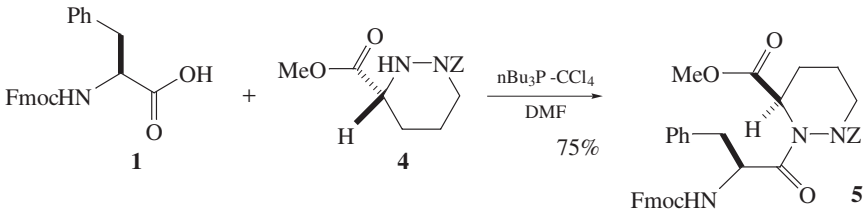
Donor	Acceptor	Product	Yield (%)
Fmoc-L-Phe-OH	HCl·H-L-Phe-OMe	Fmoc-L-Phe-L-Phe-OMe	75
Fmoc-L-Val-OH	HCl·H-L-Phe-OMe	Fmoc-L-val-L-Phe-OMe	70
Z-L-Phe-OH	HCl·H-L-Phe-OMe	Z-L-Phe-L-Phe-OMe	80
Boc-L-Pro-OH	HCl·H-L-Phe-OMe	Boc-L-Pro-L-Phe-OMe	70
Fmoc-L-Asp(Tr)-OH	HCl·H-L-Phe-OMe	Fmoc-L-Asp(Tr)-L-Phe-OMe	70
Alloc-L-Phe-OH	HCl·H-L-Pro-OMe	Alloc-L-Phe-L-Pro-OMe	75

*All reactions were carried out at room temperature with a donor:acceptor:CCl_4:nBu_3P = 1:1.5:5:3 molar ratio.

tributyl or triphenyltrichloromethylphosphonium chloride ($R_3PCCl_3 \cdot Cl$) toward the carboxylic acid, but also to more basic nature of tributyphosphine, which reacts with the amino acid hydrochlorides to generate the free amines.

This protocol was also applied with success to piperazic acid derivative **4**, which is known to show poor reactivity under conventional peptide-forming conditions such as DCC and BOP (Scheme 2). In order to examine the extent of racemization, a diastereomixture of Boc-DL-Tyr(Me)-L-Phe-OMe was synthesized using CCl_4-nBu_3P. Comparison of this mixture with Boc-L-Tyr(Me)-L-Phe-OMe, synthesized in the same manner, using ^{1}H-NMR revealed that no detectable racemization occurred. All of the dipeptides synthesized showed a single diastereomer by ^{1}H-NMR. However, two limitations were observed for the CCl_4-PBu_3 promoted peptide-forming reaction: (1) *N*-protected β-hydroxy amino acids, (e.g., threonine), form dehydroamino acids; and (2) *N*-acyl protected amino acids give unsatisfactory results.

In conclusion, it has been demonstrated that the conditions described here will be a valuable asset for coupling with urethane-protected amino acids. This method is rapid and convenient, and generates an easily separable by-product, tributylphosphine oxide.



Scheme 2.

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EXPERIMENTAL

General

Dry *N*,*N*-dimethylformamide (DMF) was purchased from Aldrich. Infrared spectra (IR) were obtained on a Perkin-Elmer 1320 infrared spectrometer. ^{1}HNMR spectra were recorded at 300 MHz. Chemical shifts are reported in parts per million (ppm). The residual solvent peak was used as an internal reference. Low-resolution mass spectra (LRMS) and high-resolution mass spectra (HRMS) were recorded in a Finnigan 90/MAT using positive chemical ionization.

General Procedure for Fmoc-L-Phe-L-Phe-Ome (3)

To a stirred solution of Fmoc-L-Phe-OH (130 mg, 0.336 mmol), HCl·H-L-Phe-OMe (195 mg, 0.504 mmol), and CCl_4 (162 μL, 1.68 mmol) in DMF (2 mL) was added nBu_3P (6) (270 μL, 1.08 mmol). After 10 min at room temperature, the reaction was concentrated *in vacuo*. The crude dipeptide was purified by silica gel chromatography (2:1:1, Hexanes:EtOAc:CH_2Cl_2) to afford Fmoc-L-Phe-L-Phe-OMe (126 mg, 0.252 mmol, 75%). (The slow addition of nBu_3P increases the product yield slightly.)

3 ^{1}H NMR (300 MHz, $CDCL_3$): 3.09 (m, 4H), 3.61 (s, 3H), 4.15 (t, 1H), 4.23 (m, 2H), 4.35 (m, 1H), 4.79 (q, 1H), 5.31 (d, 1H), 6.23 (d, 1H), 6.95–7.75 (m, 18H). HRMS (CI): calcd for $C_{34}H_{32}O_5N_2$ 549.2389, found m/z = 549.2440 $(M+H)^+$. IR: 3299.7, 3061.9, 2923.0, 1739.0, 1685.4, 1659.0, 1536.3. $[\alpha]_D$ = +15.5° (*c* 0.5, $CHCl_3$).

5 ^{1}H NMR (300 MHz, $CDCL_3$): 1.17 (t, 2H), 1.59 (s, 2H), 2.02 (s, 3H), 3.42 (m, 1H), 4.17 (m, 3H), 4.23 (m, 2H), 4.41 (m, 3H), 5.20 (m, 1H), 5.22 (s, 2H), 7.30 (m, 8H), 7.58 (t, 1H), 7.77 (m, 1H), 7.86 (t, 2H), 8.03 (t, 2H), 8.22 (d, 2H), 8.41 (d, 2H). LRMS (CI): calcd for $C_{38}H_{37}O_7N_3$ 648.2710, found m/z = 649 $(M+H)^+$. IR: 3325.4, 3058.3, 2922.7, 2854.1, 1810.9, 1718.6, 1518.8. $[\alpha]_D$ = +24.3° (*c* 0.3, $CHCl_3$).

ABBREVIATIONS

Abbreviations used: HOBt = 1-hydroxybenzotriazole; HOOBt = 3-hydroxy-1,2,3-benzotriazin-4(3H)-one; HOAt = 1-hydroxy-7-azabenzotriazol; NMM = *N*-methylmorpholine; Fmoc = 9-fluorenylmethoxycarbonyl; Z = benzyoxycarbonyl; Boc = *tert*-butoxycarbonyl; DCC = dicyclohexylcarbodiimide; BOP = bezotriazole-yloxytris(dimethylamino)phosphonium hexafluorophosphate; Alloc = allyloxycarbonyl.

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