

## A Green Synthesis of Diisopropyl Phosphoryl Amino Acid

Xiao Bin SUN, Yu Ping FENG, Xiang Feng GUO, Yu Fen ZHAO\*

The Key Laboratory of Bio-organic Phosphorus Chemistry, Education of Ministry, Department of Chemistry, School of Life Science and Engineering, Tsinghua University, Beijing 100084

**Abstract:** In this paper, we report that diisopropyl phosphoryl amino acid could be prepared with reasonable yields under solvent-free condition by adding amino acid to the mixture of diisopropyl phosphite and N-chlorodiisopropylamine.

**Keywords:** Phosphoramidates, amino acids, N-chlorodiisopropylamine, phosphorylation.

Derivatives of N-phosphoryl amino acids are of pharmaceutical and biological interest, especially as potential enzyme inhibitors<sup>1, 2, 3</sup>. Moreover, it is known that N-phosphoryl amino acid is the starting material to prepare biologically active N-phosphopeptide in many efficient methods reported recently<sup>4, 5</sup>. Thus, it is necessary to find simple and practical pathway for the synthesis of N-dialkoxyphosphoryl amino acids. Previously, we had successfully synthesized N-dialkoxyphosphoryl amino acid by adding diisopropyl phosphite (DIPPH) **1** to the aqueous-organic mixed solution containing amino acid, carbon tetrachloride and triethylamine<sup>6</sup>. Brands provided another kind of synthetic method<sup>7</sup> by dropping sodium hypochlorite to an aqueous solution of amino acid and DIPPH in the presence of sodium hydroxide. However the yield was not optimized.

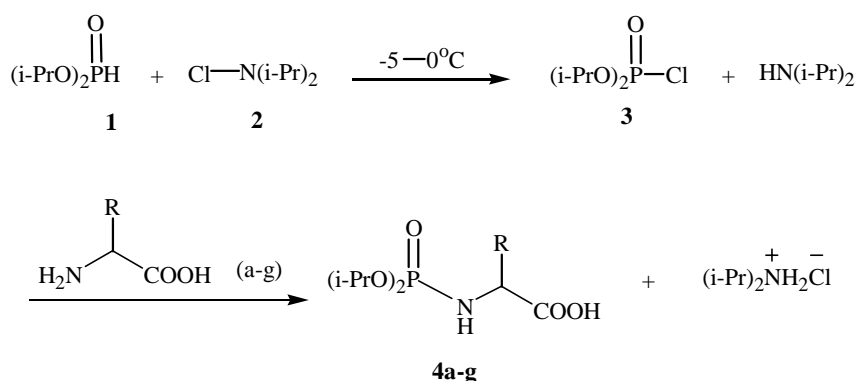
Here we describe a new method for the synthesis of diisopropyl phosphoryl (DIPP) amino acid **4a-g** with satisfactory yields *via* adding the amino acid to a reaction mixture of **1** and N-chlorodiisopropylamine<sup>8</sup> **2** (**Scheme 1**) without any solvent. The present route is friendly to the environment.

The reactions were carried out by dropping 1.5 equivalents of **2** to 1.5 equivalents of **1** at  $-5-0^{\circ}\text{C}$  within 10 minutes, then adding one equivalent of powdered amino acids in portions to the mixture. After 9 hours' stirring at  $-5-0^{\circ}\text{C}$ , acidification and extraction **4a-g** were isolated in 52-96% yields<sup>9</sup>, as shown in **Table 1**. All of them were characterized by <sup>1</sup>HNMR, <sup>13</sup>CNMR, ESI-MS spectral analysis as well as compared with authentic samples.

---

\* E-mail: tp-dch@mail.tsinghua.edu.cn

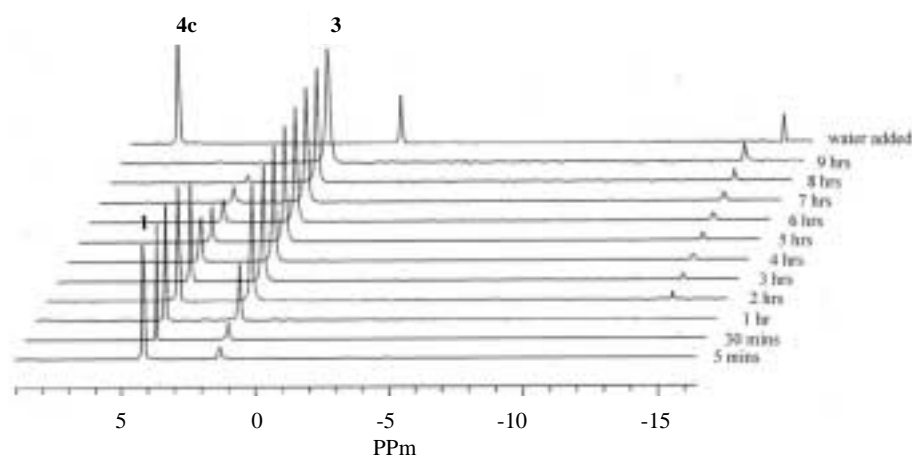
Scheme 1

Table 1 Reaction of amino acid with **1** in the presence of **2**

Product	Amino acid	Yield (%)
DIPP- Gly <b>4a</b>	Gly	93
DIPP- $\beta$ -Ala <b>4b</b>	$\beta$ -Ala	96
DIPP- <i>L</i> -Ala <b>4c</b>	<i>L</i> -Ala	88
DIPP- <i>L</i> -Try <b>4d</b>	<i>L</i> -Try	83
DIPP- <i>L</i> -Glu <b>4e</b>	<i>L</i> -Glu	77
DIPP- <i>L</i> -Leu <b>4f</b>	<i>L</i> -Leu	52
DIPP- <i>L</i> -Ileu <b>4g</b>	<i>L</i> -Ileu	54

It is worth noting that the reactions proceed under solvent-free condition, which is friendly to the environment. However, in order to optimize the yields, half molar equivalent excess of phosphorylating agent (**1+2**), low temperature (-5-0°C) and 9 hours stirring for the reaction are needed. This conclusion has been confirmed through many experiments.

**Figure 1** gave the stacking  $^{31}\text{P}$ NMR for reaction of *L*-alanine with **1** and **2**. As the reaction proceeded, the peak of the reactant **1** (4.18 ppm) was gradually decreased, and finally disappeared. Meanwhile the peak at 1.61 ppm **3**, which was coincided with the authentic sample diisopropyl phosphorochloridate<sup>10</sup>, was slowly increased. Since the products **4a-g** existed as solid during the reaction, they were not observed by  $^{31}\text{P}$ NMR. Only after water was added to quench the reaction, a new peak at 7.44 ppm showed up (last spectra). In addition, there were small peaks at 1.00, -13.98 and -14.89 ppm resulted from the hydrolysis of **3** and side-reaction. Hence the reaction mechanism was proposed as **Scheme 1**. When **1** is mixed with **2**, **3** is generated right away. Then it reacts with amino acid to produce **4a-g**. At the same time one equivalent of hydrogen chloride is neutralized by diisopropylamine generated during the reaction.

**Figure 1**  $^{31}\text{P}$ NMR stacking figure for reaction of *L*-alanine with **1** and **2**

In conclusion, the combination of **1** and **2** is characterized as a solvent-free, simple and mild phosphorylating reagent to give N-phosphoryl amino acids with reasonable yields. This method could be applied for the phosphorylation of any primary amine and alcohol, even for nucleoside, which is in progress.

### Acknowledgment

The authors would like to thank the National Natural Science Foundation of china (Grand No.20132020) for financial support, the Ministry of Science and Technology, the Chinese Ministry of Education and Tsinghua University

### Reference and Notes

1. S. Rowsell, R. A. Pauptit, A. D. Tucker, R. G. Melton, D. M. Blow, P. Brick, *Structure*, **1997**, 5, 337.
2. C. Z. Rodriguez, H. M. Holmes, K. L. Mlodnosky, V. Q. Lam, C. E. Berkman, *Bioorg. Med. Chem. Lett.*, **1998**, 8, 1521.
3. H. Y. Lu, K. L. Mlodnosky, T. T. Dinh, A. Dastgah, V. Q. Lam, C. E. Berkman, *J. Org. Chem.*, **1999**, 64, 8698.
4. S. Z. Dong, H. Fu, Y. F. Zhao, *Syn. Comm.*, **2001**, 31 (13), 2067.
5. J. N. Zeng, C. B. Xue, Q. W. Chen, Y. F. Zhao, *Bioorganic Chemistry*, **1989**, 17, 434.
6. G. J. Ji, C. B. Xue, J. N. Zeng, L. P. Li, W. G. Chai, Y. F. Zhao, *Synthesis*, **1988**, 444.
7. K. M. J. Brands, K. Wiedbrauk, J. M. Williams, U. H. Dolling, P. J. Reider, *Tetra. Lett.*, **1998**, 39, 9583.
8. A. Chandrasekaran, R. O. Day, R. R. Holmes, *Inorg. Chem.*, **1997**, 36, 2578.
9. Typical reaction procedure: Under stirring at  $-5-0^{\circ}\text{C}$  **2** (1.62 g, 12 mmol) was dropped to a flask containing **1** (1.99 g, 12 mmol) within 10 minutes. Several minutes later 8 mmol powdered amino acid **a-g** was added to the mixture in portions. Then 0.5 mL tri-ethyl amine was added 20 minutes later. After 9 hours' stirring at  $-5-0^{\circ}\text{C}$ , 10 mL water was added to the mixture and it was stirred for one hour on ice-bath. Then the solution was washed with petroleum, diethyl ether, ethyl acetate and dichloromethane successively. The

pH of the solution was adjusted to 2 by slow addition of dilute hydrochloric acid at 0°C. Sodium chloride (30 g) was then added. **4a-d** could precipitate and be obtained through filtration, whereas **4e-g** was gotten by extracting the resulting solution with ethyl acetate (3×25 mL), drying over anhydrous MgSO<sub>4</sub> and evaporating in vacuum.

10. F. R. Atherton, H. T. Howard, A. R. Todd, *J. Chem. Soc.*, **1948**, 1106.

Received 8 April, 2002