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The design and synthesis of a novel organophosphorus compound containing the structure of both β-amino acid and β-aminophosphonate

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Abstract

A novel organophosphorus compound containing the structure of both β-amino acid and β-aminophosphonate is designed and synthesized. Arbuzov reaction with $P(OEt)_3$, the *N*-Boc protected iodide **3** cannot provide the desired product but 2-oxazolidinone **4** because of the neighboring-group participation of the Boc moiety. To avoid the intramolecular participation of the carbamates, the Ts protecting group is employed and the Ts-protected iodide **5** affords the target product successfully.

Keywords: β-Amino acid; β-Aminophosphonate; Neighboring-group participation; Arbuzov reaction; Amino-protecting group

β-Amino acids (β-AAs) play a significant role in medicinal chemistry. They are the structural units of β-peptides, compounds with better pharmacological profiles than natural peptides and natural products containing β-amino acid units exhibit antibiotic, antifungal, cytotoxic, and other pharmacological properties [1,2]. On the other hand, β-aminophosphonates have received considerable attention as a result of their increasing applications in enzyme inhibitors, agrochemicals or pharmaceuticals [3,4]. In our previous work [5], we have synthesized L-phosphinothricin which is organophosphorus compound containing the structure of α-amino acid and exhibits strong herbicidal activity. The search for the preparation of organophosphorus compounds **1** is of particular interest because of its special structure of both β-amino acid and β-aminophosphonate. This compound can be synthesized from commercially available aspartic acid which has the moiety of β-amino acid. Retrosynthetic analysis is depicted in Scheme 1.

Unfortunately, when protecting group (PG) was *t*-butoxycarbonyl (Boc), the Arbuzov reaction of $P(OEt)_3$ with iodide **3** [6] did not give **1**, the desired target, but plenty of a new compound without the moiety of diethyl phosphonate. ^{1}HNMR, ^{13}CNMR and MS indicated the product was 2-oxazolidinone **4** [7]. A further experiment by only refluxing iodide **3** in a little toluene for 8 h was performed to investigate that if iodide **3** could react by itself without $P(OEt)_3$. The result showed that no 2-oxazolidinone **4** formed by TLC and the iodide **3** did not disappear either. All of these indicated that $P(OEt)_3$ should catalyze the reaction, namely the iodide **3** underwent an intramolecular reaction in the catalysis of $P(OEt)_3$ (Scheme 2).

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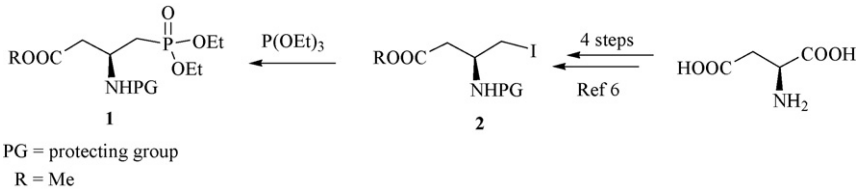
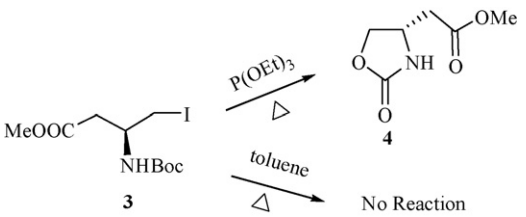


Scheme 1.



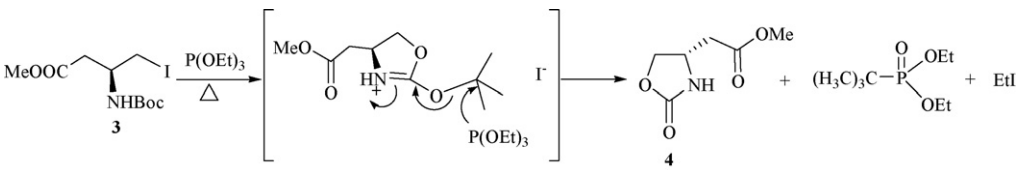
Scheme 2.

The reaction was hypothesized to be a result of intramolecular attack of the carbonyl oxygen of the Boc protecting group on the alkyl iodide to form the intermediate shown in Scheme 3 [8]. Attack of $P(OEt)_3$ on the *t*-butyl position of the intermediate afforded the unexpected product **4**.

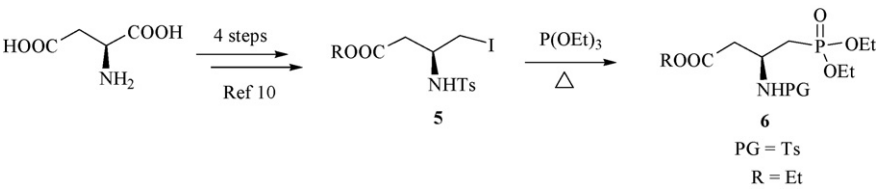
Base on this hypothesis, when the target compound **1** expected to be obtained according to the above route, the carbamates should be unsuitable to use as amino-protecting groups in iodide **2**, because these protecting groups could all perform an intramolecular reaction via neighboring-group participation. Replaced iodine group with bromine group could be an alternative strategy, but it would not avoid the intramolecular reaction essentially despite bromide had a lower reactivity [9].

So *p*-toluenesulfonyl (Ts), a non-carbamate amino-protecting group, was employed and the Ts-protected iodide **5** was designed. This compound was difficult to be synthesized from L-aspartic acid by a modification of the procedure of Ref. [6], but it can be obtained directly according to another literature procedure [10]. The following Arbuzov reaction of $P(OEt)_3$ with iodide **5** carried out very smoothly and it provided the target compound **6** [11] with 70% yield (Scheme 4).

In conclusion, the synthesis of the novel organophosphorus compound containing the structure of both β-amino acid and β-aminophosphonate has been described. It involves the Arbuzov reaction of *N*-Boc protected iodide **3** with $P(OEt)_3$ affords the unexpected 2-oxazolidinone **4** and a hypothesis of neighboring-group participation of the



Scheme 3.



Scheme 4.

carbamates has been invoked to explain the result. Moreover, when Ts, a non-carbamate amino-protecting group, is employed, the target compound has been obtained successfully.

References

[1] S. Fustero, C. del Pozo, S. Catalan, et al. Org. Lett. 11 (2009) 641.
[2] A. Jose, R.R. Paul, R. Mohan, et al. Synthesis 11 (2009) 1829.
[3] F. Palacios, A.M.O. de Retana, J. Oyarzabal, et al. J. Org. Chem. 73 (2008) 4568.
[4] F. Palacios, C. Alonso, J.M. de los Santos, Chem. Rev. 105 (2005) 899.
[5] X.S. Xu, H.B. Teng, G.F. Qiu, et al. Chin. Chem. Lett. 17 (2006) 177.
[6] C.S. Dexter, R.F.W. Jackson, J. Org. Chem. 64 (1999) 7579.
[7] Date of compound **4**: yield, 64%; m.p. 77–78 °C; $[\alpha]_D^{20}$ − 66.1 (*c* 1, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.62 (dd, 1H, *J* = 6.0 and 17.1 Hz), 2.71 (dd, 1H, *J* = 8.0 and 16.8 Hz), 3.73 (s, 3H), 4.07 (dd, 1H, *J* = 6.0 and 8.7 Hz), 4.20-4.29 (m, 1H), 4.57 (t, 1H, *J* = 8.7 Hz), 6.29 (br, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 39.55, 49.09, 52.38, 69.72, 159.53, 171.08. MS: *m*/*z* 182 $[M+Na]^+$. Anal. Calcd. for $C_6H_9NO_4$: C, 45.28; H, 5.70; N, 8.80. Found: C, 45.05; H, 5.82; N, 9.08.
[8] W.P. Malachowski, J.K. Coward, J. Org. Chem. 59 (1994) 7625.
[9] J.K. Coward, R. Lok, J. Org. Chem. 38 (1973) 2546.
[10] C. Ensch, M. Hesse, Helv. Chim. Acta 85 (2002) 1659.
[11] Date of compound **6**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.20–1.31 (m, 9H), 2.04 (dd, 2H, *J* = 18.1 and 4.5 Hz), 2.58–2.85 (m, 2H), 3.87–4.07 (m, 7H), 5.98 (d, 1H, *J* = 8.1 Hz), 7.30 (d, 2H, *J* = 7.2 Hz), 7.76 (d, 2H, *J* = 7.5 Hz). MS: *m*/*z* 422$[M+H]^+$.