

Direct synthesis of phosphinopeptides containing C-terminal α -aminoalkylphosphinic acids

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Received: 29 November 2009 / Accepted: 27 December 2009 / Published online: 22 January 2010
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Abstract A series of phosphinopeptides containing C-terminal α -aminoalkylphosphinic acids were prepared in good yields directly in one-pot reactions of 2-(*N*-benzoxycarbonylamino)alkanamides/peptide amides, aldehydes, and aryldichlorophosphines, followed by hydrolysis. In the current method, the peptide bond was formed in a Mannich-type reaction.

Keywords Amino amide · Mannich reaction · Peptide · Phosphinopeptide · Synthesis

Introduction

Phosphono-peptides and phosphino-peptides are important phosphorus analogues of naturally occurring peptides. They have been widely used as enzyme inhibitors and as haptens for catalytic antibody research because they can be considered as stable mimetics of tetrahedral transition states in ester and amide hydrolysis and formation (Kafarski and Lejczak 2000a, b; Cunningham et al. 2008). Several phosphono-peptides have also shown potent antibacterial activity (Kafarski and Lejczak 2000a, b).

The phosphonamidate bond in the phosphono-peptides have been generally formed by the reaction of phosphonochloridates with amino acid esters or peptide esters (Kafarski and Lejczak 2000a, b; Jacobsen and Bartlett

1981; Thorsett et al. 1982; Elliott et al. 1985; Bartlett and Lamden 1986; Musiol et al. 1994; Sampson and Bartlett 1988; Mucha et al. 1994; de Fatima Fernandez et al. 1995), direct condensation of phosphonate monoesters with amino acid esters or peptide esters in the presence of coupling reagents (Galeotti et al. 1996; Campbell and Bermak 1994a, b; Karanewsky and Badia 1986), and our Mannich-type condensation of benzyl carbamate, aldehydes, alkyl dichlorophosphite, and subsequent aminolysis with amino esters (Fu et al. 2006) or alcoholysis with hydroxyl esters (Xu and Gao 2005; Liu et al. 2006).

The phosphinamidate bond in the phosphino-peptides have been generally formed by the reaction of phosphinochlorides with amino acid esters or peptide esters (Moree et al. 1993; Mucha et al. 1994), direct condensation of phosphinic acids with amino acid esters or peptide esters in the presence of coupling reagents (Elhaddadi et al. 1991), the enzyme-catalyzed condensation of phosphinate ethyl esters and amino esters (Natchev 1991), and our Mannich-type condensation of *N*-Cbz protected amino amides/peptide amides, aldehydes, aryldichlorophosphines, and subsequent aminolysis with amino acid esters/peptide esters (Li et al. 2007; He et al. 2009).

Phosphono-peptides and phosphino-peptides containing C-terminal α -aminoalkylphosphonic acids or α -aminoalkylphosphinic acids have been synthesized by coupling of *N*-protected amino acids or their active esters with dialkyl α -aminoalkylphosphonates/alkyl α -aminoalkylphosphinates (Vassiliou et al. 2008; Ravaschino et al. 2006; Atherton et al. 1986), or their free acids in organic media or in aqueous-organic media (Kafarski and Lejczak 1988; Solodenko et al. 1991; Lukas et al. 2002). An alternative method for the synthesis of these type of phosphono-peptides is ammonolysis or aminolysis of 1-(*N*-chloroacetyl-amino)alkylphosphonic acids (Kudzin et al. 2008), which

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were prepared from aminoalkylphosphonates and chloroacetic acid.

Although several methods are available for the preparation of phosphinopeptides containing C-terminal α -aminoalkylphosphinic acids, most of them use the phosphinic acid derivatives as starting materials, which were generally synthesized in multi-step procedure (Kukhar et al. 1994; Soloshonok et al. 1992; Xu and Yu 1999). These methods have some disadvantages, such as complicated multi-step procedure of preparation, product isolation and purification. The overall yields from the synthesis of the phosphinic acid derivatives to the desired peptide products are seldom satisfactory. It is therefore worthy to develop a new synthetic method for the preparation of this type of important phosphinopeptides. Recently we reported novel methods for the preparation of phosphonic acid derivatives via phosphorus-Mannich-type reactions (Xu and Fu 2000, 2001; Xu and Wei 2001; Liu and Xu 2005). We also reported the Mannich-type condensation of *N*-Cbz protected amino amides/peptide amides, aldehydes, aryldichlorophosphines, and subsequent aminolysis with amino acid esters/peptide esters to synthesize phosphinopeptides, in which the phosphinoylchloride intermediates were reacted with amino esters as nucleophiles (Li et al. 2007). Moreover, to optimize the reaction conditions, the hydrolysis of a phosphinoylchloride was presented, but only for one example. We herein present its extension in the direct synthesis of phosphinopeptides containing C-terminal α -aminoalkylphosphinic acids.

Materials and methods

Melting points were obtained on a Yanaco melting point apparatus and are uncorrected. The ^1H NMR, ^{13}C NMR, and ^{31}P NMR spectra were recorded on a Varian Mercury Plus 300 (300 MHz) or Bruker 400 (400 MHz) spectrometer with TMS as an internal standard in the CDCl_3 solution. ^{31}P NMR spectra were obtained with the use of broad-band ^1H decoupling; chemical shifts are reported as ppm referenced to 85% phosphoric acid with positive shift downfield. The IR spectra were taken on a Nicolet 5700 FT-IR spectrophotometer in KBr. Mass spectra were obtained on a Bruker ESQUIRE $\sim$ LCTM ESI ion trap spectrometer. HRMS data were obtained with an Agilent LC/MSD TOF mass spectrometer. TLC separations were performed on silica gel G plates with petroleum ether (60–90°C)/ethyl acetate (1:1, v/v), and the plates were visualized with UV light.

Commercially available active carbon powder was washed with 2 mol/L HCl, ethanol twice, water twice, ethanol, deionized water, and dried at 80°C before the use in chromatography.

Aryldichlorophosphines were prepared according to literature procedure (Buchner and Lockhart 1951) and their analytical data are identical to reported ones (Buchner and Lockhart 1951; Weinberg 1975).

General procedure for the preparation of *N*-Cbz-amino amides or peptide amide (Kline et al. 2008)

To a solution of *N*-Cbz-amino acids (42 mmol) and triethylamine (6.4 mL, 4.24 g, 42 mmol) in dried THF (60 mL), dropwise ethyl chloroformate was added (4.2 mL, 4.54 g, 42 mmol) under stirring at 0°C. The resulting solution was stirred at the same temperature for 30 min. After addition of ammonia (10.8 mL), the reaction mixture was stirred for another 30 min. After removal of solvent, the residue was dissolved in ethyl acetate. The solution was washed with 20 mL of water. After concentration and cooling, colorless crystalline product was afforded from the solution. Their analytical data are identical to reported ones (*N*-Cbz-L-Ala amide, Kline et al. 2008; *N*-Cbz-L-Val amide, Dziedzic et al. 2006; *N*-Cbz-L-Phe amide, Hiskey and Jung 1963; *N*-Cbz- β -Ala amide, Rapport et al. 1947; *N*-Cbz-Gly-Gly amide, Huang and Niemann 1950).

General procedure for the direct synthesis of phosphinopeptides

To a solution of *N*-Cbz-aminoalkanamide (3.0 mmol) and aldehyde (3.5 mmol) in dried acetonitrile (10 mL), arylphosphine dichloride was added (3.5 mmol) under the nitrogen atmosphere. The resulting solution was stirred at 80°C for 12 h (for *N*-Cbz-Gly-Gly amide, stirred for 36 h). After cooling and addition of water (0.05 mL), the reaction mixture was stirred for another 12 h. After removal of solvent, the residue was separated on a pretreated active carbon powder column with a mixture of petroleum ether (30–60°C) and ethyl acetate (2:1, v/v) as an eluent to remove impurities, finally with methanol as an eluent to afford desired product, which was recrystallized from methanol (or ethanol) or a mixture of methanol (ethanol) and diethyl ether to give colorless crystal phosphinopeptide.

Phenyl[N-(R,S)-[N-(S)-benzyloxycarbonylalaninyl]-1-aminophenylmethyl]-phosphinic acid (2a)

Colorless crystals, mp 314°C (dec.), yield 75%.

IR (KBr) ν (cm^{-1}): 1,654.9 (C=O), 1,592.6 (C=O), 1,169.0 (P=O).

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ : 1.76 (s, 3H, CH_3), 4.89 (m, 2H, CH & CHP), 5.01 (m, 2H, OCH_2), 6.69 (s, 1H, NH), 7.01–7.93 (m, 15H, ArH), 7.99 (s, 1H, NH), 10.03 (s, br, 1H, POH).

^{13}C NMR (100.6 MHz, DMSO- d_6) δ : 21.2, 23.0, 60.2, 65.6, 125.9, 127.0, 127.1, 127.8, 128.1, 128.2, 128.3, 128.8, 130.0, 130.4, 133.0, 137.5, 137.6, 140.9, 170.8, 172.0.

^{31}P NMR (162.0 MHz, DMSO- d_6) δ : 22.9.

HRMS (ESI) Calcd. for $\text{C}_{24}\text{H}_{25}\text{N}_2\text{O}_5\text{NaP}$ $[\text{M} + \text{Na}]^+$ 475.1393; Found 475.1376.

Phenyl[N-(R,S)-[N-(S)-benzyloxycarbonylvalinyl]-1-aminophenylmethyl]-phosphinic acid (2b)

Colorless crystals, mp 188–196°C, yield 65%. (*S,S*):(*R,S*) = 57:43.

IR (KBr) ν (cm^{-1}): 1,690.8 (C=O), 1,649.2 (C=O), 1,239.0 (P=O).

^1H NMR (400 MHz, DMSO- d_6) major epimer δ : 0.46 (d, $J = 6.8$ Hz, 3H, CH_3), 0.55 (d, $J = 6.4$ Hz, 3H, CH_3), 1.74 (dq, $J = 6.4, 6.8, 8.4$ Hz, 1H, CH), 3.93 (dd, $J = 8.4, 8.8$ Hz, 1H, NCH), 4.97 (d, $J = 12.4$ Hz, 1H in OCH_2), 5.04 (d, $J = 12.4$ Hz, 1H in OCH_2), 5.31 (dd, $J = 10, 14.4$ Hz, 1H, CHPO), 7.10–7.52 (m, 15H, ArH), 7.68–7.73 (m, 1H, NH), 8.72 (d, $J = 7.6$ Hz, 1H, NH).

^{31}P NMR (162.0 MHz, DMSO- d_6) major epimer δ : 28.6.

^1H NMR (400 MHz, DMSO- d_6) minor epimer δ : 0.64 (d, $J = 6.8$ Hz, 3H, CH_3), 0.68 (d, $J = 6.8$ Hz, 3H, CH_3), 1.74 (dq, $J = 6.0, 6.8, 6.8$ Hz, 1H, CH), 4.02 (dd, $J = 6.0, 9.6$ Hz, 1H, NCH), 4.97 (d, $J = 12.8$ Hz, 1H in OCH_2), 5.01 (d, $J = 12.8$ Hz, 1H in OCH_2), 5.34 (dd, $J = 10.0, 14.8$ Hz, 1H, CHP), 7.10–7.52 (m, 15H, ArH), 7.68–7.73 (m, 1H, NH), 8.6 (d, $J = 9.6$ Hz, 1H, NH).

^{31}P NMR (162.0 MHz, DMSO- d_6) minor epimer δ : 29.1.

^{13}C NMR (100.6 MHz, DMSO- d_6) δ : 17.5, 18.8, 19.4, 19.6, 30.95, 30.99, 53.2 (d, $J_{\text{P-C}} = 104$ Hz), 53.3 (d, $J_{\text{P-C}} = 105$ Hz), 59.9, 60.8, 65.8, 65.9, 127.5, 128.0, 128.1, 128.2, 128.3, 128.4, 128.5, 128.72, 128.78, 128.82, 128.87, 128.9, 132.0, 132.1, 132.2, 132.3, 133.5, 136.7 (d, $J_{\text{P-C}} = 9$ Hz), 156.3, 171.3 (d, $J_{\text{P-C}} = 6$ Hz), 156.4, 171.4 (d, $J_{\text{P-C}} = 6$ Hz).

HRMS (ESI) Calcd. for $\text{C}_{26}\text{H}_{30}\text{N}_2\text{O}_5\text{P}$ $[\text{M} + \text{H}]^+$ 481.1886; Found 481.1878.

Phenyl[N-(R,S)-[N-(S)-benzyloxycarbonylphenylalaninyl]-1-aminophenyl-methyl]phosphinic acid (2c)

Colorless crystals, mp 275°C (dec.) °C, yield 70%.

IR (KBr) ν (cm^{-1}): 1,685.8 (C=O), 1,654.8 (C=O), 1,191.3 (P=O).

^1H NMR (400 MHz, DMSO- d_6) δ : 2.70 (m, 2H, CH_2), 4.30 (m, 1H, CH), 4.93 (m, 3H, OCH_2 & CHP), 7.02–7.76 (m, 22H, ArH & 2NH).

^{31}P NMR (162.0 MHz, DMSO- d_6) δ : 20.4.

HRMS (ESI) Calcd. for $\text{C}_{30}\text{H}_{30}\text{N}_2\text{O}_5\text{P}$ $[\text{M} + \text{H}]^+$ 529.1886; Found 529.1891.

Phenyl[N-(R,S)-[N-benzyloxycarbonyl- β -alaninyl]-1-aminophenylmethyl]-phosphinic acid (2d)

Colorless crystals, mp 126–132°C, yield 88%.

IR (KBr) ν (cm^{-1}): 1,715.5 (C=O), 1,675.0 (C=O), 1,252.6 (P=O).

^1H NMR (400 MHz, DMSO- d_6) δ : 2.28 (s, 2H, CH_2CO), 2.99 (s, 2H, NCH_2), 5.01 (s, 2H, OCH_2), 5.40 (s, 1H, CHP), 7.05 (s, 1H, NH), 7.34–7.60 (m, 15H, ArH), 7.70 (s, 1H, NH), 8.86 (s, 1H, POH).

^{13}C NMR (100.6 MHz, DMSO- d_6) δ : 35.8, 37.5, 53.3 (d, $J = 104.7$ Hz), 65.7, 127.5, 128.2, 128.5, 128.8, 128.9, 132.1, 132.1, 133.37, 133.44, 136.6, 137.7, 156.3, 170.2.

^{31}P NMR (162.0 MHz, DMSO- d_6) δ : 31.3.

HRMS (ESI) Calcd. for $\text{C}_{24}\text{H}_{26}\text{N}_2\text{O}_5\text{P}$ $[\text{M} + \text{H}]^+$ 453.1573; Found 453.1577.

4-Methylphenyl[N-(R,S)-[N-benzyloxycarbonyl- β -alaninyl]-1-aminophenyl-methyl]phosphinic acid (2e)

Colorless crystals, mp 179–186°C, yield 87%.

IR (KBr) ν (cm^{-1}): 1,688.8 (C=O), 1,636.2 (C=O), 1,182.2 (P=O).

^1H NMR (400 MHz, DMSO- d_6) δ : 2.26 (t, $J = 5.6$ Hz, 2H, CH_2CO), 2.39 (s, 3H, CH_3), 2.97 (t, $J = 5.6$ Hz, 2H, CH_2N), 4.99 (s, 2H, OCH_2), 5.32 (dd, $J = 10, 14.4$ Hz, 1H, CHP), 7.04 (s, 1H, NH), 7.23–7.57 (m, 15H, ArH & NH), 8.79 (s, 1H, POH).

^{13}C NMR (100.6 MHz, DMSO- d_6) δ : 21.1, 35.2, 37.0, 52.8 ($J_{\text{P-C}} = 97.3$ Hz), 65.2, 126.9, 127.3, 127.3, 127.5, 127.6, 127.7, 127.8, 128.3, 128.3, 128.4, 128.4, 128.5, 131.6, 131.7, 136.3, 137.1, 140.2, 140.8, 155.8, 169.7.

^{31}P NMR (162.0 MHz, DMSO- d_6) δ : 31.3.

HRMS (ESI) Calcd. for $\text{C}_{25}\text{H}_{28}\text{N}_2\text{O}_5\text{P}$ $[\text{M} + \text{H}]^+$ 467.1730; Found 467.1729.

Phenyl[N-(R,S)-[N-benzyloxycarbonylglycinyl]-1-amino-2-methylpropyl]-phosphinic acid (2f)

Colorless crystals, mp 274°C (dec.), yield 81%.

IR (KBr) ν (cm^{-1}): 1,728.5 (C=O), 1,660.1 (C=O), 1,236.3 (P=O).

^1H NMR (400 MHz, DMSO- d_6) δ : 0.87 (d, $J = 5.2$ Hz, 3H, CH_3), 0.95 (d, $J = 5.2$ Hz, 3H, CH_3), 2.15 (m, 1H, $\text{CH}(\text{CH}_3)_2$), 3.46 (d, $J = 12$ Hz, 1H in COCH_2), 3.65 (d, $J = 12$ Hz, 1H in COCH_2), 4.08 (m, 1H, CHPO), 5.02 (s, 2H, OCH_2), 6.26 (s, br, 1H, NH), 7.34–7.70 (m, 12H, ArH, POH & NH).

^{13}C NMR (100.6 MHz, DMSO- d_6) δ : 18.2 (d, $J_{\text{P-C}} = 4.0$ Hz), 20.9 (d, $J_{\text{P-C}} = 15$ Hz), 27.9, 43.3, 52.8

(d, $J_{\text{P-C}} = 108$ Hz), 65.4, 127.6, 127.7, 128.0 (d, $J_{\text{P-C}} = 12$ Hz), 128.3, 131.3 (d, $J_{\text{P-C}} = 10$ Hz), 131.5, 132.6 (d, $J_{\text{P-C}} = 7$ Hz), 133.8 (d, $J_{\text{P-C}} = 5$ Hz), 137.1, 156.3, 169.1.

^{31}P NMR (162.0 MHz, DMSO- d_6) δ : 23.5.

HRMS (ESI) Calcd. for $\text{C}_{20}\text{H}_{26}\text{N}_2\text{O}_5\text{P}$ $[\text{M} + \text{H}]^+$ 405.1573; Found 405.1577.

Phenyl[*N*-(*R,S*)-[*N*-(*N*-benzyloxycarbonylglycyl)]glycyl]-*l*-aminophenyl-methyl]phosphinic acid (**2g**)

Colorless crystals, mp 292°C (dec.), yield 80%.

IR (KBr) ν (cm^{-1}): 1,684.9 (C=O), 1,653.8 (C=O), 1,635.8 (C=O), 1,235.9 (P=O).

^1H NMR (400 MHz, DMSO- d_6) δ : 3.68 (m, 4H, 2NHCH₂), 4.89 (m, 1H, CHP), 5.03 (s, 2H, OCH₂), 7.05–7.65 (m, 16H, ArH & NH), 8.27 (s, br, 1H, NH).

^{13}C NMR (100.6 MHz, DMSO- d_6) δ : 42.1, 43.3, 55.4 ($J_{\text{P-C}} = 94$ Hz), 65.5, 125.5, 126.8, 126.9, 127.6, 127.7, 128.0, 128.2, 129.5, 132.1 ($J_{\text{P-C}} = 7.5$ Hz), 136.8, 139.1, 156.4, 168.3, 169.2.

^{31}P NMR (162.0 MHz, DMSO- d_6) δ : 20.1.

HRMS (ESI) Calcd. for $\text{C}_{25}\text{H}_{27}\text{N}_3\text{O}_6\text{P}$ $[\text{M} + \text{H}]^+$ 496.1632; Found 496.1632.

Results and discussion

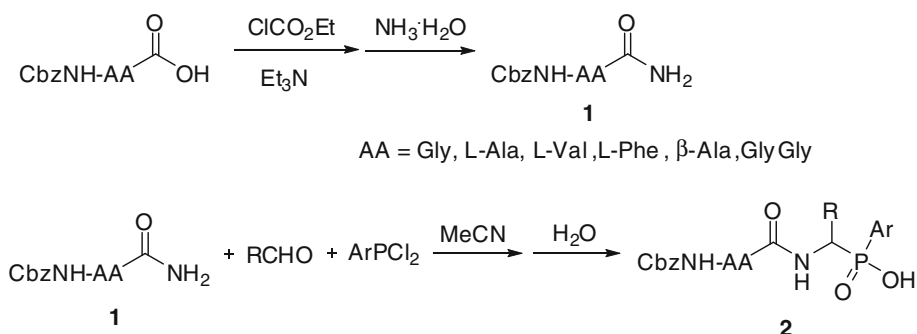
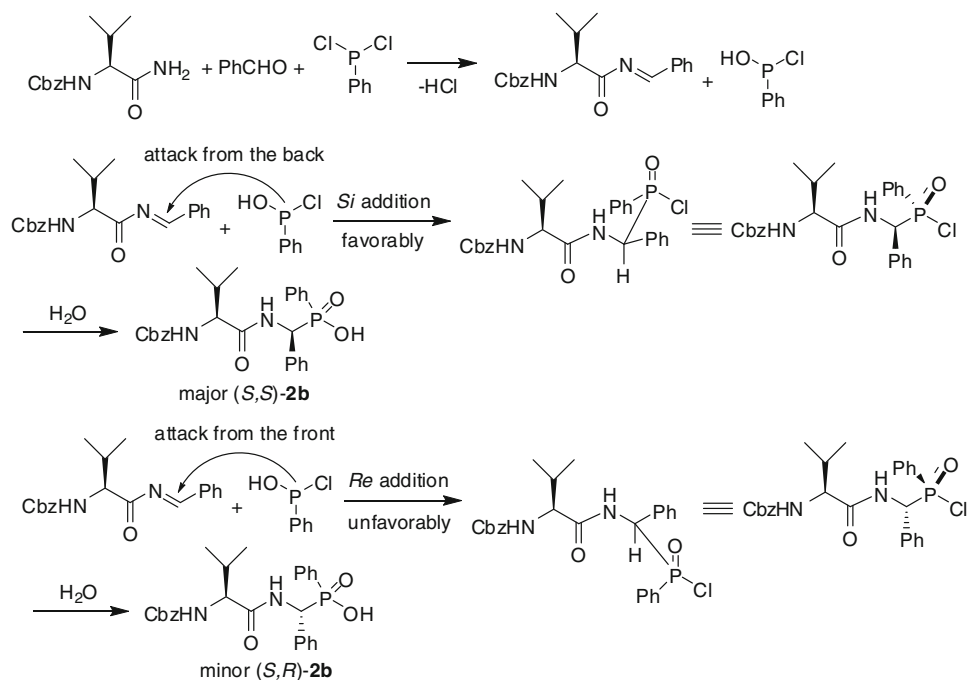
Several α -*N*-benzyloxycarbonyl(Cbz)-amino amides, a β -*N*-Cbz-amino amide (β -*N*-Cbz-alaninamide), and an *N*-benzyloxycarbonyl protected peptide amide (*N*-Cbz-glycylglycinamide) were prepared from the corresponding acids by the mixed anhydride method via activation with ethyl chloroformate and aminolysis with ammonia. The reaction of *L*- α -*N*-Cbz-alaninamide, benzaldehyde, and phenyldichlorophosphine followed by hydrolysis was selected to optimize the reaction conditions. On the basis of our previous investigation (Li et al. 2007), acetonitrile is a suitable solvent because it shows good solubility for most *N*-Cbz amino amides. After a mixture of *L*- α -*N*-Cbz-alaninamide, benzaldehyde, and phenyldichlorophosphine was refluxed in anhydrous acetonitrile for 12 h and hydrolyzed for 6 h at room temperature, the desired phosphinopeptide was generated in a good yield on the basis of TLC and ESI mass spectral analyses. However, the purification met some problem because the desired peptide is a strong polar compound, which shows strong absorbance on silica gel. After several attempts, we found that the active carbon powder is an appropriate stationary phase for such strong polar compound. After reaction and removal of solvent, the residue was separated on an active carbon powder column with gradient elute. Weak polar starting materials and

byproducts were eluted with a mixture of petroleum ether (30–60°C) and ethyl acetate (2:1, v/v). Polar peptide product was obtained with methanol as an eluent. After recrystallized from a mixture of methanol and diethyl ether or methanol, colorless crystal product was obtained in good yield. Under optimized conditions, a series of phosphinopeptides were prepared by the use of different aldehydes, *N*-Cbz-amino amides, and aryldichlorophosphines. The results are summarized in Table 1. The results indicated that the side-chain of the amino amides affects the yields obviously. Low yields were obtained for the amino amides with bulky substituents (Table 1, entries 2–3). Aliphatic aldehydes also work for the reaction (Table 1, entry 6). The reaction was further extended to an *N*-Cbz protected peptide amide, a phosphotriptide was afforded in a good yield of 80% (Table 1, entry 7). The structures of all phosphinopeptides **1** were characterized by ^1H NMR, ^{13}C NMR, ^{31}P NMR, and MS spectrometries (Scheme 1).

On stereochemistry of the product phosphinopeptides, for *N*-Cbz- β -Ala amide and *N*-Cbz-Gly-Gly amide, racemic phosphinopeptides **2d–g** were obtained. For optically active *N*-Cbz-*L*-Ala amide, *N*-Cbz-*L*-Val amide, and *N*-Cbz-*L*-Phe amide, low degree of asymmetric induction was observed because the chiral center is too far away from the reactive center in the addition step of the arylchlorophosphonous acid to the *N*-acyl imine in the reaction (Scheme 2). *N*-Cbz-*L*-Val amide shows the highest stereoselectivity in the reaction to afford phosphinopeptide **2b** with a diastereomeric ratio of 57:43 on the basis of integration in ^{31}P NMR analysis (only one peak was observed in ^{31}P NMR spectra of products **2a** and **2c** possibly because the chiral center of the amino acid moiety in these two products play an unobvious effect to their phosphorus atom due to long distance). Phenyl[*N*-(*S*)-[*N*-(*S*)-benzyloxycarbonylvalinyl]-*l*-aminophenylmethyl]phosphinic acid (**2b**) was assumed as major diastereomer on the basis of the reaction mechanism (Scheme 2). The amide, benzaldehyde, and phenyldichlorophosphine react to produce an *N*-acylimine and phenylchlorophosphonous acid as previous report (Li et al. 2007). The phenylchlorophosphonous acid then attacks the imine favorably from its *Si* side

Table 1 Direct synthesis of phosphinopeptides

Entry	Phosphinopeptide	AA	R	Ar	Yield (%)
1	2a	<i>L</i> -Ala	Ph	Ph	75
2	2b	<i>L</i> -Val	Ph	Ph	65
3	2c	<i>L</i> -Phe	Ph	Ph	70
4	2d	β -Ala	Ph	Ph	88
5	2e	β -Ala	Ph	4-MePh	87
6	2f	Gly	Me ₂ CH	Ph	81
7	2g	GlyGly	Ph	Ph	80

Scheme 1 Direct synthesis of phosphinopeptides**Scheme 2** Formation mechanism and stereostructures of diastereomeric phosphinopeptide **2b**

because the isopropyl group exists and subsequent proton transfer affords the key intermediate as the aminoalkylphosphinic chloride, which undergoes hydrolysis to generate the product phosphinopeptide with *S,S* configuration as major product. Similarly, the phenylchlorophosphonous acid attacks the imine unfavorably from its *Re* side to afford the phosphinopeptide with *S,R* configuration as minor product (Scheme 2).

On comparison with the previously reported methods, the current method is thus a direct synthetic route to these valuable peptide mimics and is a very useful and convenient method for the preparation of phosphinopeptides containing C-terminal α -aminoalkylphosphinic acids. The protocol is very simple and practical.

Conclusion

In conclusion, a direct method for the one-pot preparation of phosphinopeptides containing C-terminal α -aminoalkyl-

phosphinic acids from simple starting materials has been developed. Using this approach, phosphinopeptides containing C-terminal α -aminoalkylphosphinic acids can be conveniently prepared in good yields directly from simple chemicals. The method should prove to be valuable for organic and biological chemists interested in and required the preparation of this type of phosphorus containing peptides.

Acknowledgments The project was supported partly by National Natural Science Foundation of China (No. 20092013 and 20772005).

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