ORGANIC LETTERS

2009
Vol. 11, No. 17
3922−3925

First and Convergent Synthesis of Hybrid Sulfonophosphinopeptides

Fengdan He,[‡] Fanhua Meng,[†] Xiuqing Song,[§] Wenxiang Hu,[‡] and Jiaxi Xu*,[†]

State Key Laboratory of Chemical Engineering Resource, Faculty of Science, Beijing University of Chemical Technology, Beijing 100029, P. R. China, Department of Chemistry, Capital Normal University, Beijing100048, P. R. China, and College of Life Science and Bio-engineering, Beijing University of Technology, Beijing100124, China

jxxu@mail.buct.edu.cn

Received July 6, 2009

ABSTRACT

Hybrid sulfonophosphinopeptides were first and convergently synthesized in satisfactory to good yields via the Mannich-type reaction of N-protected 2-aminoalkanesulfonamides, aromatic aldehydes, and aryldichlorophosphines and subsequent aminolysis with amino esters.

Phosphonopeptides and phosphinopeptides have been widely used as enzyme inhibitors, haptens for production of catalytic antibodies, and antibacterial and herbicidal agents during the last two decades.[1] To date, several efficient synthetic routes have been developed for synthesis of phosphonopeptides and phosphinopeptides.[2] The formation methods of the phosphinamide bond in phosphinopeptides generally include the reaction of N-protected aminoalkylphosphinic chlorides with amino acid esters or peptide esters,[3] the direct condensation of aminoalkylphosphinic acids and amino esters or peptide esters in the presence of coupling reagents, such as DCC, BOP, DPPA, with additives HOBt or DMAP, in low yields,[4] the enzyme-catalyzed coupling reaction of ethyl aminoalkylphosphinate and amino esters in satisfactory yields,[5] and the Mannich ligation of amino amides, aldehydes, aryldichlorophosphines, and amino/peptide esters.[6]

Sulfonopeptides, as a class of more stable analogues of naturally occurring or synthetic peptides, have also been used as enzyme inhibitors.[7] The sulfonopeptide bond has been generally formed through two pathways. One is the reaction of N-protected aminoalkanesulfonyl chlorides with amino acid esters or peptide esters.[8] The other is the condensation of N-protected aminoalkanesulfinyl chlorides and amino esters or peptide esters, followed by subsequent oxidation.[9] However, no hybrid sulfonophosphonopeptide, composed of amino acid, aminoalkylphosphonic acid or aminoalkylphos-

---

[‡] Capital Normal University.

[†] Beijing University of Chemical Technology.

[§] Beijing University of Technology.

(1) (a) For a review, see: Kafarski, P.; Lejczak, B. The Biological Activity of Phosphono- and Phosphinopeptides. In *Aminophosphonic and Aminophosphinic Acids: Chemistry and Biological Activity*; Kukhar, V. P., Hudson, H. R., Eds.; John Wiley: Chichester, 2000; Chapter *12*, pp 404−442. (b) For a recent example, see: Ravaschino, E. L.; Docampo, R.; Rodriguez, J. B. *J. Med. Chem.* **2006**, *49*, 426–435. (c) Ntai, I.; Phelan, V. V.; Bachmann, B. O. *Chem. Commun.* **2006**, 4518–4520. (d) Cunningham, E.; Drag, M.; Kafarski, P.; Bell, A. *Antimicrob. Agents Chemother.* **2008**, *52*, 3221–3228.

(2) For a review, see: Kafarski, P.; Lejczak, B. The Biological Activity of Phosphono- and Phosphinopeptides. In *Aminophosphonic and Aminophosphinic Acids: Chemistry and Biological Activity*; Kukhar, V. P., Hudson, H. R., Eds.; John Wiley: Chichester, 2000; Chapter *12*, pp 173−204.

(3) (a) Moree, W. J.; van der Marel, G. A.; van Boom, J. H.; Liskamp, R. M. J. *Tetrahedron* **1993**, *49*, 11055–11064. (b) Mucha, A.; Kafarski, P.; Plenat, F.; Cristau, H.-J. *Tetrahedron* **1994**, *50*, 12743–12754.

(4) Elhaddadi, M.; Jacquier, R.; Petrus, C.; Petrus, F. *Phosphorus Sulfur Silicon* **1991**, *63*, 255–259.

(5) Natchev, I. A. *Tetrahedron* **1991**, *47*, 1239–1248.

(6) Li, B. N.; Cai, S. Z.; Du, D. M.; Xu, J. X. *Org. Lett.* **2007**, *9*, 2257–2260.

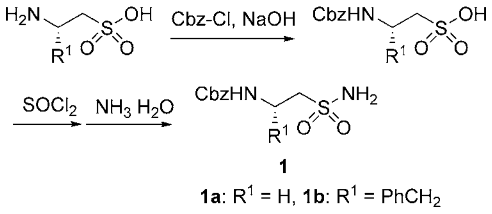
10.1021/ol901543y CCC: $40.75

phinic acid, and aminoalkanesulfonic acid residues, has been synthesized until now. Herein, we report the first and convergent synthesis of sulfonophosphinopeptides via the Mannich-type reaction of N-protected 2-aminoalkanesulfonamides, aldehydes, and aryldichlorophosphines and subsequent aminolysis with amino esters.

Previously, we used the Mannich-type reactions of carbamates or amino amides, aldehydes, and chlorophosphites, or aryldichlorophosphines and subsequent aminolysis with amino or peptide esters to prepare phosphonopeptides[10] and phosphinopeptides[6] or alcoholysis with hydroxyl esters or hydrolysis to give rise to depsiphosphonopeptides.[10,11] In the current method, we have substituted sulfonamides as the amine component in the Mannich-type reaction with aldehydes and aryldichlorophosphines to generate hybrid sulfonophosphinopeptides in a one-pot pseudo-four-component condensation reaction (Scheme 2). To the best of our knowledge, this is the first synthesis of hybrid sulfonophosphinopeptides. The synthetic method is a convergent and atom-economic strategy for synthesis of sulfonophosphinopeptides.

We have recently reported several efficient routes to prepare structurally diverse substituted taurines (2-aminoalkanesulfonic acids).[12] In a manner similar to the previously reported method,[13] N-protected 2-aminoalkanesulfonamides **1a** and **1b** were prepared from the corresponding 2-aminoalkanesulfonic acids by protection of the amino group with benzyl chloroformate under basic conditions, conversion of the sulfonic acid to the sulfonyl chloride with thionyl chloride, and subsequent aminolysis with ammonia (Scheme 1).

Scheme 1. Synthesis of N-Protected 2-Aminoalkanesulfonamides **1**



We initially optimized the reaction of the sulfonamide **1a** with benzaldehyde and 4-methylphenyldichlorophosphine in anhydrous acetonitrile and subsequent aminolysis with ethyl glycinate hydrochloride or ethyl glycinate (Scheme 2, R^1 = H, R^2 = Ph, Ar = 4-MePh, AA = Gly). After several attempts (Table 1, entries 1−3), a hybrid sulfonophosphinopeptide **3a** was obtained in good yield (Table 1, entry 3). We then explored the use of other N-protected 2-aminoalkanesulfonamide, aromatic aldehyde, aryldichlorophosphine, and amino acid ethyl ester components in this reaction (Table 1). The results indicate that different aromatic aldehydes and aryldichlorophosphines show similar reactivity (Table 1, entries 3−6). However, the product yield obviously depends on the steric hindrance of aminoalkanesulfonamides and amino esters (Table 1, entries 4, 7, 9, and 10). 2-Aminoethanesulfonamide (**1a**) and ethyl glycinate show higher yields than (*S*)-2-amino-3-phenylpropanesulfonamide (**1b**) and ethyl (*S*)-leucinate.

Scheme 2. Synthesis of Sulfonophosphinopeptides **3**

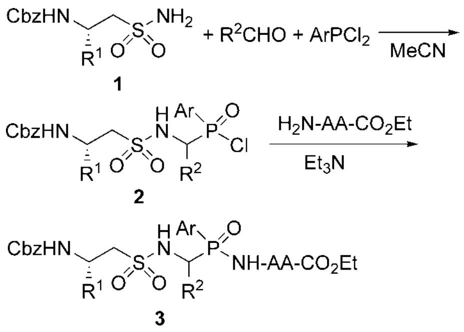


Table 1. Synthesis of Sulfonophosphinopeptides[a]

entry	peptide	R^1	R^2	Ar	AA	yield[b] (%)
1	**3a**	H	Ph	4-MePh	Gly	30[c]
2	**3a**	H	Ph	4-MePh	Gly	43[d]
3	**3a**	H	Ph	4-MePh	Gly	75
4	**3b**	H	Ph	Ph	Gly	65
5	**3c**	H	4-MePh	Ph	Gly	74
6	**3d**	H	4-ClPh	Ph	Gly	70
7	**3e**	Bn	Ph	Ph	*β*-Ala	62
8	**3e**	Bn	Ph	Ph	*β*-Ala	60[e]
9	**3f**	Bn	4-ClPh	Ph	Gly	60
10	**3g**	Bn	Ph	Ph	(*S*)-Leu	56

[a] The reaction was conducted in a molar ratio of sulfonamide/aldehyde/$ArPCl_2$ of 1.9:2.0:2.0 at 45 °C for 12 h first and then stirred for 24 h after addition of an amino ester (6.0 mmol) and TEA (8.0 mmol). [b] Isolated yield. [c] The reaction was conducted in a molar ratio of sulfonamide/aldehyde/$ArPCl_2$ of 2.4:2.7:2.7 with GlyOEt•HCl (8.0 mmol) and TEA (8.0 mmol). [d] The reaction was conducted as in footnote c with GlyOEt (8.0 mmol). [e] DIPEA was used instead of TEA.

---

(7) (a) For a review, see: Xu, J. X. *Chin J. Org. Chem.* **2003**, *23*, 1–9. (b) For an example, see: Carson, K. G.; Schwender, C. F.; Shroff, H. N.; Cochran, N. A.; Gallant, D. L.; Briskin, M. J. *Bioorg. Med. Chem. Lett.* **1997**, *7*711−714.

(8) (a) Lowik, D. W. P. M.; Liskamp, R. W. J. *Eur. J. Org. Chem.* **2000**, 1219–1228. (b) Luisi, G.; Calcagni, A.; Pinnen, F. *Tetrahedron Lett.* **1993**, *34*, 2391–2392. (c) Gude, M.; Piarulli, U.; Potenza, D.; Salom, B.; Gennari, C. *Tetrahedron Lett.* **1996**, *47*, 8589–8592. (d) Gennari, C.; Salom, B.; Potenza, D.; Williams, A. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2067–2069.

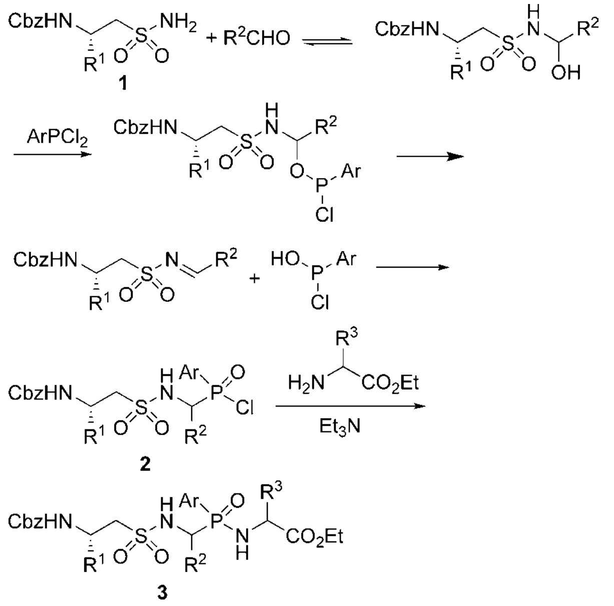
(9) (a) Moree, W. J.; van der Marel, G. A.; Liskamp, R. M. J. *Tetrahedron Lett.* **1991**, *32*, 409–412. (b) Moree, W. J.; van Gent, L. C.; van der Marel, G. A.; Liskamp, R. M. J. *Tetrahedron* **1993**, *49*, 1133–1150. (c) Moree, W. J.; van der Marel, G. A.; Liskamp, R. M. J. *Tetrahedron Lett.* **1992**, *33*, 6389–6392. (d) Moree, W. J.; van der Marel, G. A.; Liskamp, R. M. J. *J. Org. Chem.* **1995**, *60*, 5157–5169.

(10) Fu, N. Y.; Zhang, Q. H.; Duan, L. F.; Xu, J. X. *J. Peptide Sci.* **2006**, *12*, 303–309.

(11) (a) Xu, J. X.; Gao, Y. H. *Synthesis* **2005**, 783–788. (b) Liu, H.; Cai, S. Z.; Xu, J. X. *J. Peptide Sci* **2006**, *12*, 337–340.

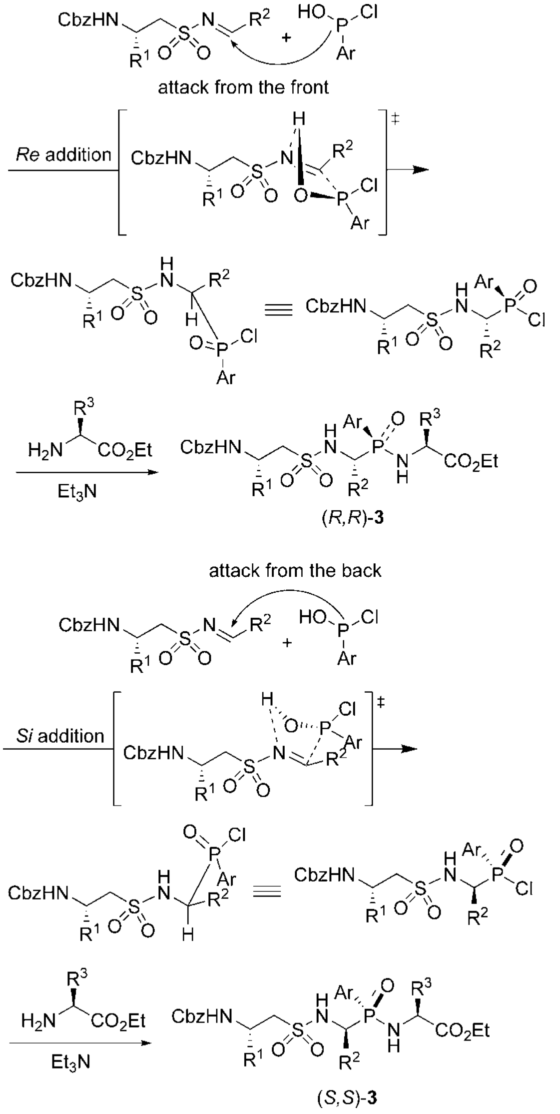
As for the reaction mechanism, in a manner similar to previous one in the synthesis of phosphinopeptides,[6] it was assumed that a sulfonamide first attacks an aldehyde to form an *N*-sulfonylaminohydrin adduct, which further reacts with an aryldichlorophosphine to produce an aryl chlorophosphite. The phosphite undergoes an elimination to give rise to an *N*-sulfonylimine and an arylchlorophosphonous acid. The arylchlorophosphonous acid undergoes an addition to the *N*-sulfonylimine to produce the key intermediate as the aminoalkylphosphinic chloride, which undergoes an aminolysis with an amino ester to generate the final product hybrid sulfonophosphinopeptide (Scheme 3).

Scheme 3. Proposed Mechanism in the Formation of Hybrid Sulfonophosphinopeptides in the Mannich-Type Reaction



^1H, ^{13}C, and ^{31}P NMR spectra of sulfonophosphinopeptides **3a−d** show that only one of the two possible diastereomeric pairs was produced, indicating that only a pair of enantiomers was generated in each of the reactions for 2-aminoethanesulfonamide (**1a**). However, for reactions with (*S*)-2-amino-3-phenylpropanesulfonamide (**1b**) as the amine component, a pair of peaks were observed in ^{31}P NMR spectra of its products in each of reactions, indicating that a pair of diastereomers were generated for sulfonophosphinopeptides **3e−g**. On the basis of the integretion of ^{31}P NMR spectra, no obvious stereoselectivity 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*-sulfonylimine. The similar stereoselectivity was also observed in the synthesis of phosphinopeptides in our previous investigation.[6] The newly formed stereocenters in sulfonophosphinopeptides **3** are generated in the addition step in the mechanism. Thus, their configurations could be deduced from the addition mechanism (shown in Scheme 4). In the addition step, the arylchlorophosphonous acid could attack the *N*-sulfonylimine from either its *Re* side or *Si* side via a five-membered ring transition state formed through a hydrogen bond (N−H−O), producing (*R*,*R*)- and (*S*,*S*)-arylaminoarylmethylphosphinic acid chloride **2**. (*R*,*S*)- and (*S*,*R*)-isomers cannot be generated due to the five-membered transition state control. For reactions with (*S*)-2-amino-3-phenylpropanesulfonamide (**1b**) as the amine component, because the chiral

Scheme 4. Stereochemical Control in Synthesis of Sulfonophosphinopeptides



---

(12) (a) Xu, J. X. *Tetrahedron: Asymmetry* **2002**, *13*, 1129–1134. (b) Xu, J. X.; Xu, S. *Synthesis* **2004**, 276–282. (c) Huang, J. X.; Wang, F.; Du, D. M.; Xu, J. X. *Synthesis* **2005**, 2122–2128. (d) Huang, J. X.; Du, D. M.; Xu, J. X. *Synthesis* **2006**, 315–319. (e) Hu, L. B.; Zhu, H.; Du, D. M.; Xu, J. X. *J. Org. Chem.* **2007**, *72*, 4543–4546. (f) Zhang, W.; Wang, B. Y.; Chen, N.; Du, D. M.; Xu, J. X. *Synthesis* **2008**, 197–200. (g) Wang, B. Y.; Zhang, W.; Zhang, L. L.; Du, D. M.; Liu, G.; Xu, J. X. *Eur. J. Org. Chem.* **2008**, 350–355. (h) Yu, H.; Cao, S. L.; Zhang, L. L.; Liu, G.; Xu, J. X. *Synthesis* **2009**, 2205–2209. (i) Chen, N.; Zhu, M.; Zhang, W.; Du, D. M.; Xu, J. X. *Amino Acids* **2009**, *37*, 309–313.

(13) (a) Hara, T.; Durell, S. R.; Myers, M. C.; Appella, D. H. *J. Am. Chem. Soc.* **2006**, *128*, 1995–2004. (b) Brouwer, A. J.; Merks, R.; Dabrowska, K.; Rijkers, D. T. S.; Liskamp, R. M. J. *Synthesis* **2006**, 455–460.

center is too far away from the reactive center no obviously steric difference is generated in *Re* and *Si* additions. The hydrogen bond plays a crucial role in the stereochemical control in the addition step in the mechanism. After nucleophilic displacement with amino acid esters, sulfonophosphinopeptides **3** were obtained. Thus, arylaminoarylmethylphosphinic acid residues in sulfonophosphinopeptides should be (*R*,*R*) or (*S*,*S*). That is, sulfonophosphinopeptides **3a**−**d** are a pair of enantiomers with (*R*,*R*) and (*S*,*S*) configurations. Sulfonophosphinopeptides **3e**−**f** are a pair of diastereomers with (*S*,*R*,*R*) and (*S*,*S*,*S*) configurations. And sulfonophosphinopeptide **3g** is a pair of diastereomers with (*S*,*R*,*R*,*S*) and (*S*,*S*,*S*,*S*) configurations.

In summary, a series of hybrid sulfonophosphinopeptides, composed of amino acid, aminoalkylphosphinic acid, and aminoalkanesulfonic acid residues, were synthesized in satisfactory to good yields via the Mannich-type reaction of N-protected 2-aminoalkanesulfonamides, aromatic aldehydes, and aryldichlorophosphines, and subsequent aminolysis with amino esters. The current synthetic route is a convergent and atom-economic method. It is an efficient pathway to prepare hybrid sulfonophosphinopeptides from simple starting materials.

Acknowledgment. This work was supported in part by the National Natural Science Fundation of China and the Beijing Natrual Science Foundation (Project No. 2092022).

Supporting Information Available: Experimental procedure, analytical data, and copies of ^{1}H NMR and ^{13}C NMR spectra of N-protected 2-aminoalkanesulfonamides and sulfonophosphinopeptides. This material is available free of charge via the Internet at http://pubs.acs.org.

OL901543Y