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Solid Phase Synthesis of Phosphinopeptoids as Transition State Analog Inhibitors

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Abstract: A procedure for preparing novel phosphinopeptoids, **1**, on a solid support is described. The key step in the synthesis includes a conjugate addition of the trivalent form of a protected aminomethylphosphinic acid (**5**) to a resin-bound acrylate. © 1998 Elsevier Science Ltd. All rights reserved.

Protease inhibitors have been studied as regulatory agents for a number of different diseases.[1] Previous reports on the solid phase synthesis of protease inhibitors include proposed transition-state analog[2] inhibitors such as hydroxyethylenes,[3] diols,[4] sulfonamides,[5] and phosphonate esters.[6] Phosphorus-containing compounds are some of the most potent known inhibitors of metallo-[7] and aspartyl proteases.[8] Moreover, phosphinate-containing compounds are potent and chemically stable protease inhibitors and are not prone to hydrolysis as are the analogous phosphonamidates and phosphonate esters. Secondly, peptoids[9] can mimic both peptides and non-peptides, demonstrate potent and specific biological activity, are stable to a variety of proteolytic enzymes, and lack the asymmetric carbon atoms of peptides.[10,11] This communication outlines the combination of a peptoid-like backbone with a phosphinate moiety to provide a unique and versatile solid-phase synthesis of phosphinopeptoids (figure 1) starting with a resin-bound acrylic ester.

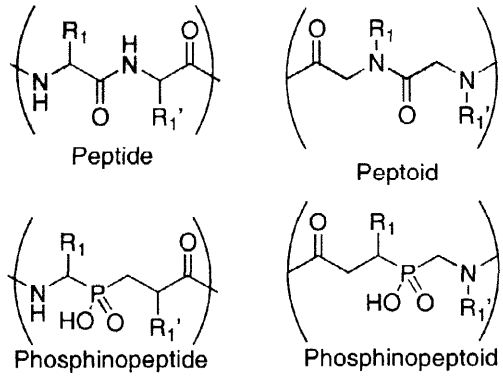

Figure 1

The fundamental strategy of the solid-phase synthesis of phosphinopeptoids (**1**) includes the use of simple and readily available starting materials. These starting materials encompass various acrylic acids, an N-protected glycine phosphinic acid, and a variety of electrophiles to cap the deprotected terminal nitrogen (Figure 2). The essential glycine derivative, aminomethylphosphinic acid, is easily synthesized in multigram quantities via literature methods.[12,15c] The key step in the synthesis involves a conjugate addition of the trivalent form of a protected aminomethylphosphinic acid to the resin-bound acrylate.

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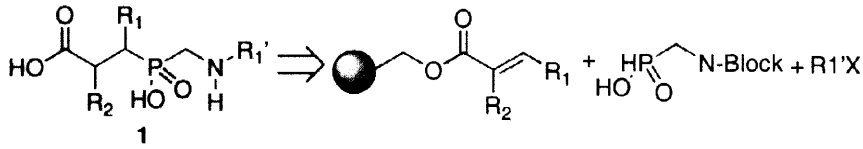
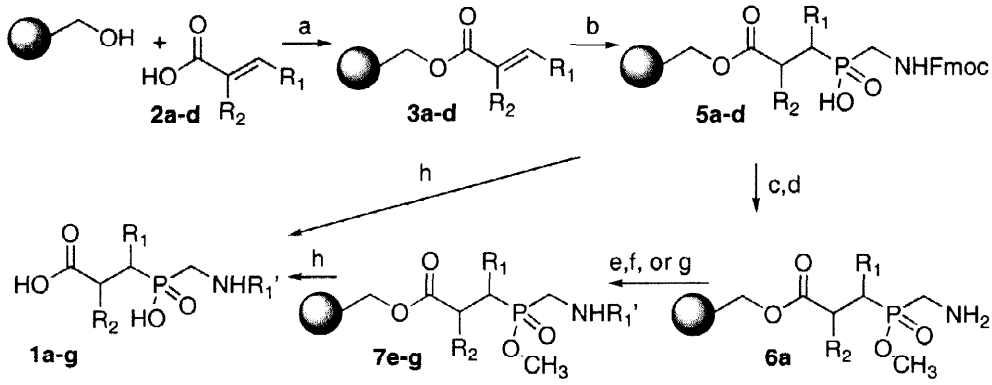
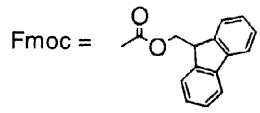


Figure 2

The synthesis of **1** is illustrated in Scheme 1. Mitsunobu condensation[13] of Wang resin and acrylic acids **2a-d** with triphenylphosphine and diethylazodicarboxylate (DEAD) in THF overnight at room temperature afforded resin-bound acrylic esters **3a-d**. The resin was shown to contain the acrylic ester by single bead solid-phase IR spectroscopy.[14] Aminomethylphosphinic acid was condensed with succinate ester of 9-fluorenylmethylcarboxylate in acetonitrile and aqueous sodium carbonate to form the 9-fluorenylmethyl (Fmoc) protected aminomethylphosphinic acid (**4**) in 75% yield. Conjugate addition of **4** to the resin-bound acrylic esters **3a-d** was accomplished by treatment of **3a-d** in degassed dichloromethane (CH_2Cl_2) with an excess of bis(trimethylsilyl)acetamide (BSA) and **4**, consecutively.[15] The reaction mixture was shaken overnight, the resin was washed with CH_2Cl_2 and methanol, sequentially, and the entire cycle was repeated. The target phophinopeptides **1a-d** were liberated from the resin with trifluoroacetic acid (TFA) in CH_2Cl_2, followed by purification by flash chromatography over silica gel with 2.5%H_2O/CH_3CN.[16] The overall yield decreased with increasing steric bulk at R1.[17]



#	R1	R2	R1'
a	H	H	Fmoc
b	CH3	H	Fmoc
c	H	CH3	Fmoc
d		H	Fmoc
e	H	H	
f	H	H	
g	H	H	



Scheme 1: a) Ph_3P, DEAD, THF; b) $PO_2H_2CH_2NHFmoc$ (**4**), bis-trimethylsilylacetamide, CH_2Cl_2; c) CH_2N_2, Et_2O, THF; d) 10% piperidine, DMF; e) benzoyl chloride, Hunig's Base, CH_2Cl_2; f) p-toluenesulfonyl chloride, DMAP, CH_2Cl_2; g) isopropylNCO, THF; h) TFA, CH_2Cl_2.

Attempts to deprotect the N-Fmoc of resin bound **5a** and directly functionalize the resultant amine proved unsuccessful due to cleavage of the resultant amino acid from the resin. Presumably, the phosphinate oxyanion was acting as an internal nucleophile to cleave the Wang ester linkage under these conditions. Therefore, elaboration at R1' was accomplished by first protecting phosphinic acid **5a** as the methyl ester by treatment with diazomethane, followed by deprotection of the Fmoc moiety by treatment with 10% piperidine in DMF to give the resin bound amino ester **6a**. Amine **6a** was then treated with an acyl chloride, a sulfonyl chloride, or an isocyanate to yield the resin bound amide (**7e**), sulfonamide (**7f**), or urea (**7g**) at R1', respectively. Treatment of **7e-g** with TFA in CH_2Cl_2 concomitantly cleaved the carboxylic acid from the resin and the phosphorus methyl ester to liberate the desired phosphinopeptoids **1e-g** in purified yields of 22, 30, and 44%, respectively for the six-step process.[18]

In summary, the solid-phase synthesis of novel phosphinopeptoids, **1**, has been accomplished for the first time. This synthesis incorporates an N-protected amino phosphinic acid moiety (**5**) on the resin by conjugate addition to an acrylic acid. Resin bound **5** can be cleaved from the resin or, after protection of the phosphinic acid and cleavage of the Fmoc, the amine terminus can be elaborated further to form **1**. These results establish the utility of solid phase synthesis of an interesting and unique class of potential transition-state analogs. Furthermore, these results expand the spectrum of chemistry that can be used to prepare libraries that are useful for enzyme inhibitor development.

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16. The purity of the crude products 7a-d were > 85% by ^{1}HNMR. No major by-products were detected. Purification was performed by flash chromatography over silica gel with 2.5%H_2O/CH_3CN to determine accurate yields of 7a-d with > 95% purity.

17. The yields for **1a-d** were 90, 48, 40, and 17% respectively.

18. The purity of the crude products 7e-g were > 85% by ^{1}HNMR. No major by-products were detected. Purification was performed by flash chromatography over silica gel with 2.5%H_2O/CH_3CN to determine accurate yields of 7e-g with > 95% purity.