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Multiple Solid Phase Synthesis of *(RS)*-1-Aminophosphinic Acids

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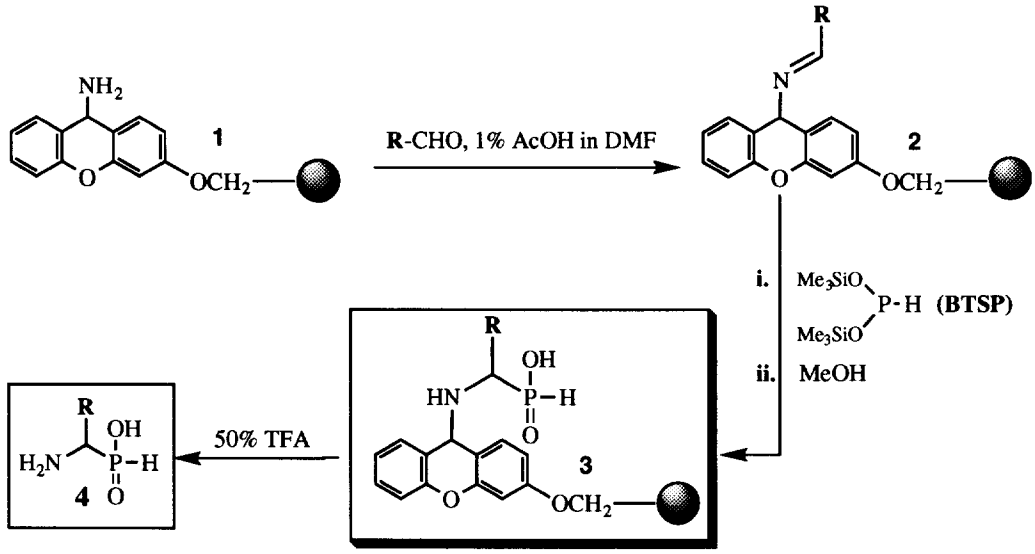
Abstract: *Novel resin bound (RS)-1-aminophosphinic acids, prepared by the facile addition of bis(trimethylsilyl)phosphonite to 9-aryl or alkylimino-xanthen-3-yloxymethyl polystyrene, on acidolysis afforded (RS)-1-aminophosphinic acids in high yields and purities.*

Solid phase synthesis has attracted much attention recently, due in part to its potential for the generation of molecular diversity within the context of combinatorial chemical libraries.[1] These chemical libraries have furnished unprecedented numbers of novel entities which can be screened for potential biological activities.[1,2] Many of the early libraries were peptide based, however to ensure molecular diversity non-natural amino acid derivatives are of increasing interest for incorporation into libraries. In this letter we report solid phase methodology for the synthesis of resin bound 1-aminophosphinic acids. These novel resin bound molecules are suitable for further elaboration and have potential for incorporation into unique combinatorial chemical libraries.

We previously reported conditions for the synthesis of substituted phosphinic acids.[3] This synthesis relies on the *in situ* generation of *bis*(trimethylsilyl)phosphonite (BTSP) followed by formation of a new carbon-phosphorus bond by Michael type addition to an appropriate electrophile such as α,β-unsaturated ketones and esters[3a] or alkylation with an appropriate alkyl iodide[3b]. In a recent useful extension of this methodology, Jiao *et al.* have prepared (*RS*)-1-aminophosphinic acids by the addition of BTSP to imines in solution.[4] 1-Aminophosphinic acid containing molecules have demonstrated their ability to modulate biochemical processes, in particular by enzyme inhibition. Examples of 1-aminophosphinic acid containing enzyme inhibitors include the therapeutic agent fosinopril[5] an angiotensin-converting enzyme (ACE) inhibitor, and the more recently reported HIV protease,[6] and stromelysin-1 (MMP-3)[7] inhibitors. 1-Aminophosphinic acid containing molecules have also found novel drug delivery applications, for example to stabilise peptide drugs during their intranasal absorption.[8] Novel multiple synthetic procedures which enable rapid preparation of structurally diverse 1-aminophosphinic acid analogues are therefore of considerable use and interest.

Our strategy for the multiple construction of 1-aminophosphinic acids is based on solid phase methodologies, and exploits the recently established[9] facile procedure for the synthesis of resin bound imines **2** prepared by the condensation of an appropriate aldehyde with 9-amino-xanthen-3-yloxymethyl polystyrene **1**.[10] The key synthetic step involves the nucleophilic addition of BTSP, readily obtained by heating hexamethyldisilazane with ammonium phosphinate under an inert atmosphere,[3] to **2** which (on methanolic work-up) results in the resin bound 1-aminophosphinic acids **3** (Scheme 1). Thus, the overall outcome of the synthetic strategy is the generation of a new phosphorus-carbon bond by the addition of BTSP to resin bound aryl or alkylimines under very mild conditions.



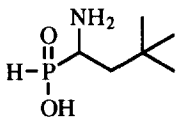
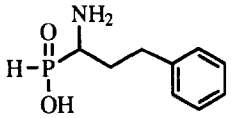
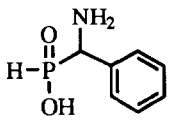
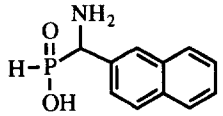
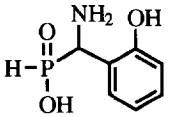
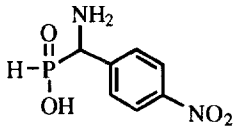
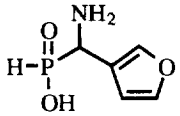
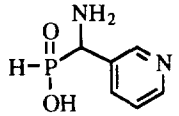
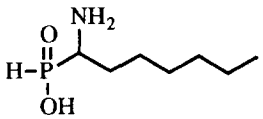
Scheme 1. Solid phase assembly of 1-aminophosphinic acids

To assess the purity and synthetic efficiency of this methodology, the (*RS*)-1-aminophosphinic acids **4** were selectively cleaved from the resin using 50% v/v trifluoroacetic acid (TFA) in CH_2Cl_2, and isolated after trituration with diethyl ether as crystalline solids. Table 1 shows the results obtained for a series of aliphatic and aromatic 1-aminophosphinic acids. Generally high yields of the aminophosphinic acids were obtained demonstrating that the reaction of BTSP with resin bound imines **2** is an efficient process, and that the imino/amino xanthene-anchor (N-C) bond is stable to the reaction conditions.

The purity of the directly isolated products was established using various analytical techniques including ^1H and ^{31}P NMR and mass spectrometric analysis. Particularly, ^1H NMR spectroscopy clearly shows the presence of a down-field doublet (~δ7.0) resonance signal with a large coupling constant of (~550 Hz) which is indicative of a P-H bond. ^{31}P NMR gives a useful indication of 'phosphorus purity' and demonstrated that no phosphonic acid contamination which would result from oxidation of the phosphinic acid product had occurred. As expected, initial indication suggests that the nucleophilic addition of BTSP to **2** is achiral. Hence, the fact that racemic mixtures are obtained makes this methodology of particular use in initial combinatorial applications due to the potential for the generation of maximal stereoisomeric molecular diversity.

In our early attempts to prepare certain simple aliphatic 1-aminophosphinic acids we met with limited success. This was rationalised as due to either incomplete formation or breakdown of the labile resin bound imine **2**. In certain cases a improved yields of 1-aminophosphinic acid was obtained if trimethyl orthoformate was used as a solvent instead of DMF when forming the imine **2**. It has been proposed that the trimethyl orthoformate is acting as a desiccant and prevents hydrolysis of the resin bound imine.[11] In certain cases the reaction failed if trimethyl orthoformate was not used as the solvent and gave respectable yields on inclusion, for example **13**, Table 1.

Table 1.

	**5** 93%[a], δ23.1.[b]		**9** 81%, δ21.0.
	**6** 90%, δ19.6.		**10** 71%, δ19.5.
	**7** 98%, δ15.1.		**11** 98%, δ17.7.
	**8** 76%, δ14.4.		**12** 100%, δ16.1.
	**13**[c] 75%, δ21.7.		

[a] % yield; [b] ^{31}P NMR chemical shift relative to H_3PO_4 (101 MHz, D_2O)
[c] Trimethyl orthoformate used as the solvent instead of DMF.

In conclusion, a simple and convenient procedure for the synthesis of (*RS*)-1-aminophosphinic acids on solid support has been established. We believe that this is the first report of direct incorporation of phosphinic-containing entities onto a resin.[12] The main advantage of this solid phase methodology is that highly pure products can conveniently be prepared on a small scale in multiple reaction vessels. Furthermore, the resin bound phosphino amino-acids **3** are ripe for exploitation in the preparation of unique peptidomimetic combinatorial libraries.

Typical Experimental Procedure

9-Arylimino-xanthen-3-yloxymethyl polystyrene was prepared as previously reported.[9] Typically, *N*-fluorenylmethoxycarbonyl-9-amino-xanthen-3-yloxymethyl polystyrene (150 mg, 0.05 mmol functionalised loading) was packed into a glass column and *N*-Fmoc-deprotected using 20% piperidine in DMF. The resin was washed extensively with DMF and an appropriate aldehyde (0.2 mmol) and glacial AcOH (1% v/v) were added to the deprotected resin suspended in DMF. The resin suspension was then gently agitated for 30 minutes and subsequently washed with DMF. The aldehyde/glacial AcOH treatment was repeated to ensure complete formation of the imine.

A preformed solution of BTSP[3] in dry CH_2Cl_2 (1.0 M, 1 mL) was then added directly to the suspension of **2** in a minimum amount of DMF. Following gentle stirring overnight, the solution was siphoned off and the resin treated with MeOH (10 mL), and washed with CH_2Cl_2 (25 mL) to yield the resin bound aminophosphinic acid **3**. **3** was then treated with TFA:CH_2Cl_2:$^iPr_3SiH$ (50:50:2 v/v, 10 mL) for 30 minutes, filtered and the filtrate was evaporated to dryness. Trituration of the residual material with diethyl ether exclusively afforded the desired 1-aminophosphinic acids as crystalline solids.

References and Notes

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12. Recently the first solid phase synthesis of phosphinic peptides was reported, however the phosphinic acid was introduced as part of a larger fragment in contrast to direct formation of a new phosphorus-carbon bond reported in this letter. Campagne, J-M.; Coste, J.; Guillou, L.; Heitz, A.; Jouin,P.*Tetrahedron Lett.*, **1993**, 34, 4181-4184.

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