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Facile Synthesis of Functionalised Phenylphosphinic Acid Derivatives

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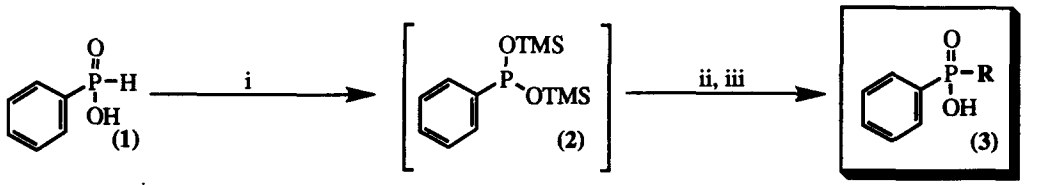
Abstract: Functionalised phenylphosphinic acid derivatives have been synthesised by addition of bis(trimethylsilyl)phenylphosphonite 2 to a series of electrophiles.

Molecules incorporating the phenylphosphinic acid motif have demonstrated their importance in a variety of useful biological and non-biological applications. Their mechanism of biological action is generally due to either enzyme inhibition, for example as interleukin-1β converting enzyme inhibitors,[1] or by being isosteric analogues of endogenous neurotransmitters, for example possessing $GABA_B$ antagonist activity.[2] Phenylphosphinic acid derivatives have also been evaluated for antibacterial activity[3,4] and show protection against fungal infection caused by *Fusarium*.[4a] Non-biological phenylphosphinic acid applications are often based on the ability of phenylphosphinic acid derivatives to form relatively stable complexes with metals.[5,6,7] In the context of metal coordination phenylphosphinic acid derivatives are also notable for their capacity to form polymeric layered complexes with *d*-block metals.[7] Phenylphosphinic acid derivatives have recently found applications in the preparation of novel heterocyclic systems either directly[8] or by rearrangement reactions.[9]

Using existing methods for the synthesis of phenylphosphinic acid derivatives only a limited selection of products are available,[10] because to date there have been no reports of standard methodology for their preparation under mild conditions. Commonly, synthesis results in the preparation of phosphinate esters which require de-esterification to liberate the free phosphinic acids. In this letter we describe general synthetic conditions suitable for the direct preparation of an array of functionalised phenylphosphinic acid derivatives under mild and flexible conditions. The synthesis relies on the *in situ* preparation of *bis*(trimethylsilyl)phenylphosphonite **2**[11] and its addition to various electrophiles, which after work-up result in functionalised phenylphosphinic acid derivatives of generic structure **3** (Scheme 1).

We have previously reported conditions for the synthesis of symmetrical and unsymmetrical phosphinic acids using *in situ* generated *bis*(trimethylsilyl)phosphonite (BTSP) under mild conditions.[12,13] In one report BTSP was prepared by the addition of an excess of triethylamine and trimethylsilyl chloride to a solution of triethylammonium phosphinate.[12] Recently we found that if phenylphosphinic acid **1** is treated with an excess of triethylamine and trimethylsilyl chloride, *bis*(trimethylsilyl)phenylphosphonite **2** is generated, which can form new carbon-phosphorus bonds by the addition to appropriate electrophiles, Scheme 1.



(i) Et_3N or $Pr^i_2EtN/TMSCl$, CH_2Cl_2, 0°C, Ar, 1-2 h (ii) Electrophile, 0°C-RT (iii) Acidic work-up

Scheme 1. Prepartion of functionalised phenylphosphinic acid derivatives.

α,β–Unsaturated esters reacted efficiently with **2** by Michael-type addition to produce 3-carboxyethyl(phenyl)phosphinic acid derivatives, (**4-8**) generally in high yield, (Table 1). Substitution of the double bond resulted in relatively, slightly lower yields, probably because addition is less favourable due to steric and electronic effects. As expected the addition of **2** to substituted unsaturated esters resulted in racemic mixtures of phosphinic acids (**6-8**). When acrylamide was used as an electrophile problems were encountered isolating the phenylphosphinic acid **9** due to appreciable aqueous solubility. An alternative non aqueous work-up was developed for water soluble products in which a 25% methanolic THF solution was used to hydrolyse the silyl-phosphorus esters resulting after reaction of **2** with an electrophile. After removal of the solvent the free phosphinic acids were isolated and washed with hexane.

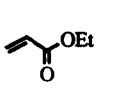
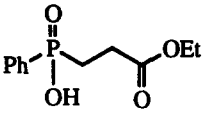
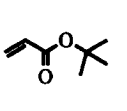
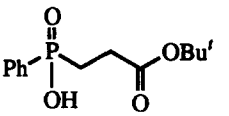
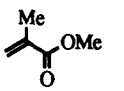
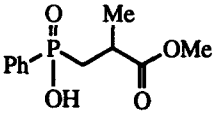
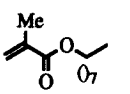
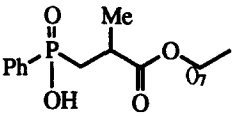
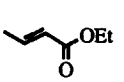
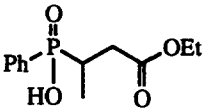
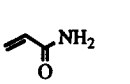
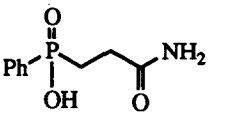
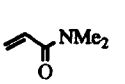
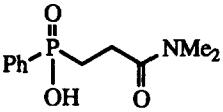
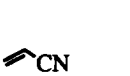
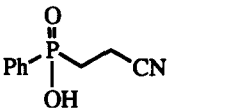
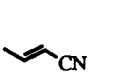
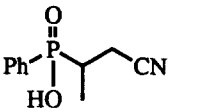
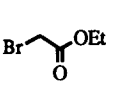
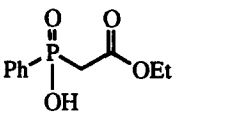
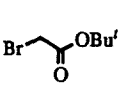
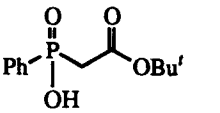
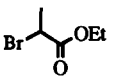
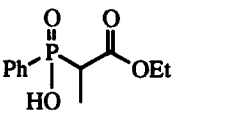
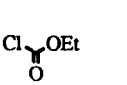
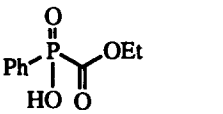
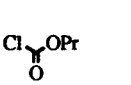
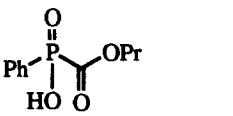
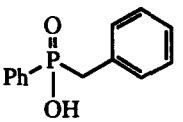
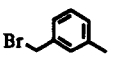
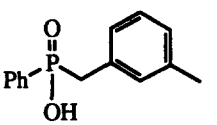
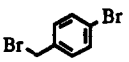
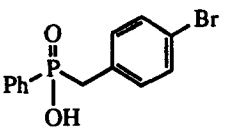
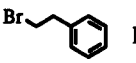
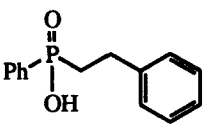
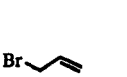
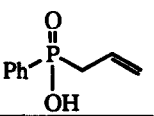
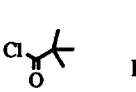
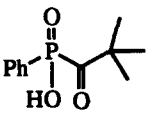
Attempts to react **2** with various brominated esters and benzyl bromides met with limited success. Under the conditions developed for the preparation of 3-carboxyethyl(phenyl)phosphinic acid derivatives above, triethylamine alkylation was found to be a significant problem using 'activated electrophiles' (as typified by entries **13-23,** Table 1). It was subsequently found that the use of the more sterically hindered *N,N*-diisopropylethylamine (Hunnigs base) significantly improved the yield. Hence under these conditions **2** generated using Hunnigs base generally reacted efficiently with a variety of electrophiles, Table 1, (**10-23**). Washing the products with hexane (sometimes containing ether) was found to be the most convenient and efficient method for purification of the functionalised phenylphosphinic acids, (which are not generally amenable to purification by flash chromatography).

The use of Hunnigs base also improved yields of phenylphosphinic acids (**10-12**) when *N,N*-dimethylacrylamide and acrylonitrile derivatives were used as electrophiles. The phenylphosphinic acids **11** and **12** can be hydrogenated to the corresponding 3-aminopropyl(phenyl)phosphinic acid derivatives;[2] 3-aminopropyl(phenyl)phosphinic acid has previously shown to have potent and selective antagonist modulatory activity at $GABA_B$ receptors.[2] Hence, this methodology offers a concise route to advanced 3-aminopropyl(phenyl)phosphinic acid precursors, offering advantages over previous routes to their preparation.[2]

2-Carboxymethyl(phenyl)phosphinic acid derivatives (**13-15**) were prepared in excellent yields using the Hunnigs base methodology detailed above. However in certain cases it was found advantageous to add an extra equivalent of Pr^i_2EtN/TMS-Cl after 12 h to ensure complete reaction. For example the yield of **15** was approximately 70% after 12 h (based on starting phenylphosphinic acid) however on addition of the extra equivalents of reagents and an additional 12 h reaction time, **15** was subsequently obtained in a yield of 97% after work-up. The 1-Carboxy(phenyl)phosphinic acids **16** and **17** represent a previously unreported class of phosphinic acid and were prepared in excellent yields. ***CAUTION:*** The addition of chloroformates to **2** is an exothermic process which requires controlled addition with suitable reaction cooling.

Activated 'bromo-electrophiles' (as typified by entries **18-22**, Table 1) generally reacted efficiently with **2** to give functionalised phenylphosphinic acids (**18-22**). However for the preparation of certain phenylphosphinic acid derivatives prolonged reaction times were necessary to drive the reactions to completion. For example, on preparation of benzyl(phenyl)phosphinic acid **18** after 12 h the yield was approximately 20% (based on starting phenylphosphinic acid), 40% after 24 h and a yield of 91% was obtained upon work-up after 48 h. The low yield for **21** is probably due to the electrophile being relatively less reactive.

Table 1. Synthesis of functionalised phenylphosphinic acid derivatives
Base: Triethylamine (4-9), Hunnigs Base (10-23)

Electrophile	Phosphinic acid		Electrophile	Phosphinic acid	
		(4) 96%[a] δ=45[b]			(5) 94% δ=46
		(6) 81% δ=44			(7) 78% δ=44
		(8) 74% δ=48			(9) 48%[c] δ=38[d]
		(10) 74% δ=44			(11) 82%[c] δ=40
		(12) 90% δ=36			(13) 98% δ=36
		(14) 94% δ=37[d]			(15) 97%[e] δ=40
		(16) 86%[f] δ=12			(17) 80%[f] δ=12
BnBr		(18) 91%[g] δ=42			(19) 98% δ=42
		(20) 44% δ=38[d]			(21) 50% δ=46
		(22) 71% δ=43			(23) 100% δ=21

[a] Percentage yield [b] ^{31}P NMR, chemical shift relative to 85% H_3PO_4 (101 MHz, $CDCl_3$) [c] Water soluble, non-aqueous work-up
[d] NMR solvent CD_3OD [e] After 12 h addition of extra TMS-Cl, Pr^i_2EtN and ethyl 2-bromopropionate
[f] *CAUTION:* exothermic reaction on addition of electrophile, controlled cooling to 0°C required [g] Reaction time 48 h

Under these general reaction conditions **2** reacted quantitatively with trimethylacetyl chloride yielding the previously unreported phenylphosphinic acid **23**. Attempts to react **2** with certain less substituted acid chlorides were unsatisfactory due to competing reactions and resulted in multiple byproduct formation.

In conclusion, this letter describes the development of synthetic methodology for the preparation of functionalised phenylphosphinic acid derivatives under mild, flexible and convenient conditions. This methodology allows the preparation of certain unreported and previously inaccessible functionalised phenylphosphinic acid derivatives.

Experimental Procedure

To a solution of phenylphosphinic acid (2.0 g, 14.1 mmol) in dichloromethane (30 ml) was added either triethylamine or diisopropylethylamine (29.6 mmol) and trimethylsilyl chloride (29.6 mmol) at 0°C under argon. The solution was stirred at room temperature for 2-3 h, cooled to 0°C and the appropriate electrophile (15.5 mmol) was added. After 12-24 h the reaction was filtered and depending on the aqueous solubility of the product the filtrate was worked up by either of two ways. For products with limited aqueous solubility the filtrate was washed with hydrochloric acid (2 M, 2x 20-30 ml) and dried. For products with significant aqueous solubility the solvent was removed *in vacuo* and the residue dissolved in MeOH/THF (1:3, 30 ml) with stirring for 30 mins. Finally for both methods removal of the solvent *in vacuo* yielded the substituted-phenylphosphinic acids which were generally washed with hexane.

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References and Notes

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