A VERSATILE ROUTE TO SUBSTITUTED PHOSPHINIC ACIDS

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Abstract: Mono-substituted phosphinic acids, symmetrical and unsymmetrical disubstituted phosphinic acids have been conveniently synthesized by 1,4 addition to α,β -unsaturated esters of bis(trimethylsilyl)phosphonite generated in situ, under very mild conditions.

Phosphinic acids are of growing importance in understanding and modulating biological processes.¹ For example, they constitute stable mimics of the tetrahedral transition states involved in amide bond formation^{1d} or hydrolysis, and can thus function as transition state analogue enzyme inhibitors. Novel routes to substituted phosphinic acids are therefore of considerable interest.²

Classical methods for phosphinic acid synthesis utilizing the Arbuzov reaction,³ involving dialkyl phosphonites and an appropriate alkylating agent, often involve harsh reaction conditions. Recently a mild procedure has appeared for the conversion of mono-substituted phosphinic acids to disubstituted phosphinic acids, *via* addition of an intermediate silyl phosphonite to activated conjugated systems.⁴

We wish to report a synthesis of both symmetrical and unsymmetrical substituted phosphinic acids involving sequential 1,4 addition of bis(trimethylsilyl)phosphonite⁵ to α,β -unsaturated esters. Bis(trimethylsilyl)phosphonite (2), which was easily prepared *in situ* from triethylammonium phosphinate (1), constitutes an equivalent to the synthon (3). Preparation, isolation and use of bis(trimethylsilyl)phosphonite^{5,6} was found to be undesirable due to the extreme pyrophoric nature of (2), and so *in situ* generation⁷ was used as shown in Scheme 1, and found to be much more convenient.

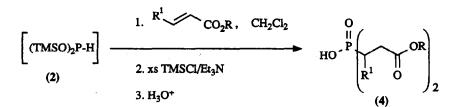
Scheme 1.

$$\begin{array}{c} \text{xs TMSCl/Et}_{3}\text{N} \\ \text{HNEt}_{3}\text{H}_{2}\text{PO}_{2} \xrightarrow{\text{CH}_{2}\text{Cl}_{2}} \\ \text{(1)} \end{array} \qquad \qquad \left[(\text{TMSO})_{2}\text{P-H} \right] \implies \qquad \begin{array}{c} \text{O} \\ \text{O} \\ \text{P} \\ \text{O} \\ \text{I} \\ \text{OH} \\ \text{(3)} \end{array}$$

For the synthesis of symmetrical disubstituted phosphinic acids (4) the appropriate acrylate was added to a solution of bis(trimethylsilyl)phosphonite (2) prepared *in situ* from (1) using an excess of chlorotrimethylsilane (TMSCl)/triethylamine⁸ solution in dichloromethane at 0 °C, and stirred overnight at room temperature, followed by simple acidic work-up. The results for symmetrical bis-addition are shown in Table 1, and the reaction in Scheme 2.

Synthesis of mono-substituted phosphinic acids was achieved by starting with a five-equivalent excess of (2) over the acrylate. The large excess of bis(trimethylsilyl)phosphonite had only a limited



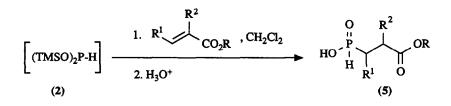




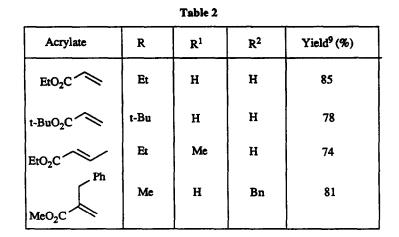
Acrylate	R	R ¹	Yield ⁹ (%)	
MeO ₂ C	Ме	н	90	
EtO ₂ C	Et	н	82	
t-BuO ₂ C	t-Bu	н	78	
EtO ₂ C	Et	Et	77	

amount of acrylate with which to react, hence no contamination with disubstituted phosphinic acid resulting from a second addition to acrylate was observed. Simple acidic work-up resulted in mono-substituted phosphinic acids (5) as viscous, colourless oils. The reaction is shown in Scheme 3, and examples in Table 2.

Scheme 3.



Synthesis of unsymmetrical disubstituted phosphinic acids was achieved by taking a previously synthesized mono-substituted phosphinic acid (5), and subjecting it to the silylating conditions $(TMSCl/NEt_3)^8$ to form the probable intermediate (6), followed by addition of the chosen acrylate and acidic work-up, to give the appropriate disubstituted phosphinic acid (7) (Scheme 4). Examples are shown in Table 3.



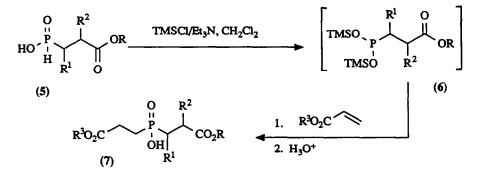


Table	3
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Mono-substituted Phosphinic acid (5)		acrylate	Disubstituted Phosphinic acid (7)	yield ⁹ (%)	
R	R ¹	R ²		R ³	
t-Bu	н	н	EtO2C	Et	75
Me	н	Bn	t-BuO ₂ C	t-Bu	63
Et	Ме	н	t-BuO ₂ C	t-Bu	77

Typical Experimental Procedure.^{9,10}

1. Symmetrical disubstituted phosphinic acids (4).

To a stirred solution of (1) (1.0 g, 5.99 mmol) in dry CH_2CI_2 (30 ml) at 0 °C, was added a 1:1 mixture of chlorotrimethylsilane and triethylamine (TMSCI/Et₃N)⁸ (6.0 ml, 18 mmol, 3.5 eq. of each), at less than 5 °C. After 1-2 h the acrylate (2.2 eq.) was added at 0 °C, stirred for 0.5 h, allowed to warm to room temperature and stirred overnight. The reaction was filtered, dilute hydrochloric acid added, and extracted with CH_2CI_2 to give the crystalline disubstituted phosphinic acid (4) which was purified by trituration with hexane/ether.

2. Mono-substituted phosphinic acids (5).

To a stirred solution of (1) (5.0 g, 29.9 mmol, 5 eq.) in dry CH_2Cl_2 (100 ml) at 0 °C, was added a 1:1 mixture of chlorotrimethylsilane and triethylamine (20 ml, 12 eq.). The acrylate (1.0 eq.) was added at 0 °C, stirred for 0.5 h, then allowed to warm to room temperature overnight. The reaction was filtered and dilute hydrochloric acid work-up followed by dichloromethane extraction yielded the phosphinic acid (5) as an oil.

3. Unsymmetrical disubstituted phosphinic acids (7).

To a solution of the appropriate mono-substituted phosphinic acid (5) (4.0 mmol, 1 eq.) in dry CH_2Cl_2 (30 ml) was added a 1:1 mixture of chlorotrimethylsilane and triethylamine (7 ml, 4 eq.) at 0 °C. After stirring for 1 h the appropriate acrylate (4.4 mmol, 1.1 eq.) was added, the reaction allowed to warm to room temperature, and stirred overnight. Filtration followed by acidic work-up and dichloromethane extraction yielded the disubstituted phosphinic acid (7) which was purified by trituration with hexane/ether.

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REFERENCES AND NOTES.

- (a) L. Maier, Phosphorus and Sulfur, 1983, 14, 295.
 (b) E.W. Petrillo, and M.A. Ondetti, Med. Res. Rev., 1982, 2, 1.
 (c) W.H. Parsons, A.A. Patchett, H.G. Bull, W.R. Schoen, D. Taub, J. Davidson, P.L. Combs, J.P. Springer, H. Gadebusch, B. Weissberger, M.A. Valiant, T.N. Mellin and R.D. Buschl., J. Med. Chem. 1988, 31, 1772.
 (d) P.A. Bartlett and W.B. Kezer, J. Am. Chem. Soc., 1984, 106, 4282.
- 2. J.K. Thottatil, C.A. Przybyla and J.L. Moniot, Tetrahedron Lett., 1984, 25, 4737.
- G.M. Kosolapoff and L. Maier, "Organic Phosphorus Compounds", Wiley-Interscience, New York, 1973, 6, p 14.
- 4. J.K. Thottathil, D.E. Ryono, C.A. Przybyla, J.L. Moniot and R. Neubeck, *Tetrahedron Lett.*, 1984, 25, 4741.
- 5. M.G. Voronkov, L.Z. Marmur, O.N. Dolgov, V.A. Pestunovich, E.I. Pokrovskii, and Y.I. Popel, J. Gen. Chem. USSR (Engl. Trans.), 1971, 41, 2005.
- 6. (a) D. Grobelny, Synthesis, 1987, 942.
 (b) P. Majewski, Synthesis, 1987, 555.
- 7. T. Hata, H. Mori and M. Sekine, Chemistry Letters, 1977, 1431.
- TMSCl/Et₃N, equivalent molar amounts, were mixed under nitrogen and centrifuged to allow removal of the supernatant, leaving behind a (copious) triethylammonium chloride precipitate.
- Satisfactory IR, NMR (¹H, ¹³C, and ³¹P), MS and/or elemental analysis were obtained for all new compounds.
- 10. All the apparatus was meticulously dry and clean. All reactions were carried out under a dry nitrogen atmosphere.

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