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Synthesis of Alkyl Phosphinic Acids from Silyl Phosphonites and Alkyl Halides[1]

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Abstract: *Mono- and di-substituted phosphinic acids have been synthesised in a one-pot reaction, by the addition of alkyl halides to silyl phosphonites, under mild and flexible conditions.*

Phosphinic acids are finding use, increasingly, as biologically active molecules.[3-6] However, most methods for their preparation[1,7] are not general, and new methods using milder conditions are required. The Arbuzov reaction[7] has often been used for the synthesis of dialkyl phosphinic acids; however, this reaction suffers from severe limitations. High reaction temperatures are required (120-160 °C) using neat reagents, and often the alkyl halide by-products are more reactive than the original electrophile, causing side-reactions. Also, only primary halides can generally be used, otherwise elimination competes with substitution. Owing to these limitations, only simple, robust electrophiles have proved useful for preparation of phosphinic acids, and additional functionality is not generally tolerated.

The Arbuzov reaction of silyl alkylphosphonites has been successful using reactive bromoacetates as electrophiles.[8] More recently, the reaction of bis(trimethylsilyl)phosphonite (BTSP) (1) with alkyl halides in refluxing benzene has been reported to give symmetrical dialkylphosphinic acids.[9] However, this was limited to certain highly reactive halides (benzyl, allyl and α-carbonyl), simple primary and methyl halides being unsatisfactory, and clearly the use of this solvent system is undesirable.

We have recently reported a method for the preparation of γ-keto-substituted phosphinic acids from BTSP (1) generated *in situ* under very mild and flexible conditions.[10] We have now extended this methodology to allow synthesis of phosphinic acids using simple alkyl halides as the electrophiles at low temperature in dichloromethane. In this Letter we wish to report the synthesis of mono-alkyl- and both symmetrical and unsymmetrical dialkyl-phosphinic acids in a one-pot reaction under mild conditions.

Mono-alkylphosphinic acids (2) were prepared by the addition of an appropriate alkyl halide to BTSP (1) in dichloromethane at room temperature. The BTSP was generated *in situ* from ammonium phosphinate and hexamethyldisilazane (HMDS) as described previously[10] (Scheme 1). Either the free phosphinic acids or adamantanammonium phosphinate salts[10] could be prepared, depending upon the work-up, and the results are shown in Table 1. Some of the free mono-alkylphosphinic acids are water soluble oils, and hence the 1-adamantanammonium salts afforded a convenient means of isolation.

Scheme 1.

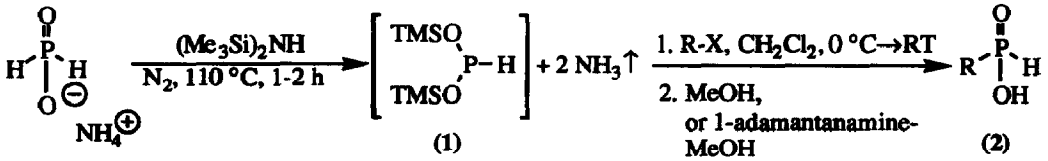
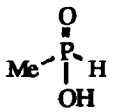
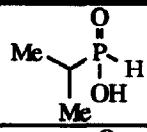
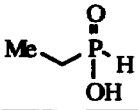
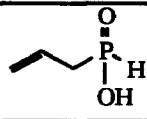
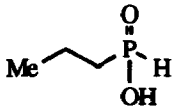
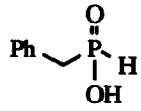
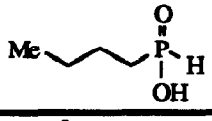


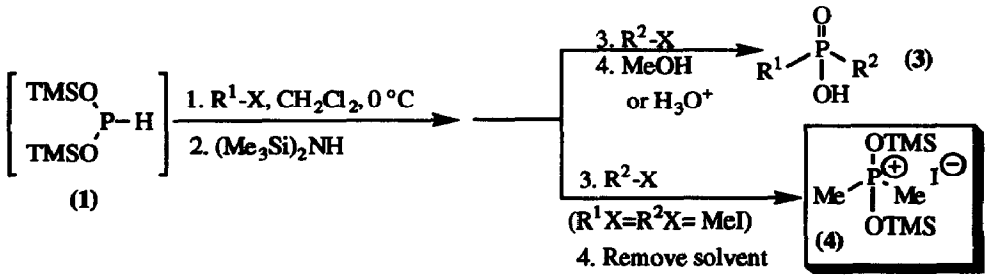
Table 1. Preparation of Mono-Alkyl Phosphinic Acids[11]

Alkyl Halide	Alkyl Phosphinic Acid (2)	Yield (%)	Alkyl Halide	Alkyl Phosphinic Acid (2)	Yield (%)
MeI		82 97[a]	*i*-PrI		58
EtI		71 95[a]	Allyl bromide		100
n-PrI		81	Benzyl bromide		98
n-BuI		88 93[a]			

[a]Yield obtained as adamantanammonium phosphinate salt

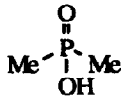
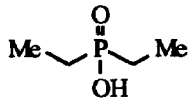
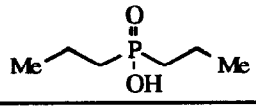
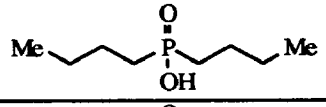
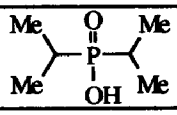
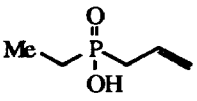
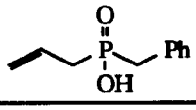
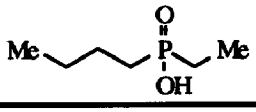
Dialkylphosphinic acids (3) could be formed by adding a second equivalent of HMDS to the reaction mixture followed by a second alkyl halide, before work-up (Scheme 2). The second electrophile could be different to the first, and hence both symmetrical and unsymmetrical dialkylphosphinic acids could be formed in a one-pot reaction (Table 2).

Scheme 2.



Unsaturated esters and acrylonitrile could also be used as electrophiles together with alkyl halides, in a sequential fashion, to give unsymmetrical disubstituted products *via* Michael-type addition plus alkylation in one pot (results not shown).

Table 2. Preparation of Dialkyl Phosphinic Acids[11]

Alkyl halide R^1X	Alkyl halide R^2X	Dialkyl Phosphinic Acid (3)	Yield (%)
MeI	MeI		52[a]
EtI	EtI		75
n-PrI	*n*-PrI		87
n-BuI	*n*-BuI		82
i-PrI	*i*-PrI		67
EtI	allyl bromide		90
allyl bromide	benzyl bromide		80
n-BuI	EtI		87

[a]Relatively low yield is due to high water solubility and difficulty of isolation (crude yield 99 %)

Alkylation reactions involving silyl phosphonites are generally believed to follow an Arbuzov-type mechanism,[8,9] where the intermediate phosphonium cation undergoes nucleophilic attack by the halide ion at silicon, giving the phosphinate ester product. In previous work this hypothetical intermediate was not detectable by ^{31}P nmr.[8] However in our work, when methyl iodide was used in Scheme 2 and the solvent removed before hydrolysis, a crystalline solid was isolated in quantitative yield, which was identified by mass spectrometry as the phosphonium intermediate (4). This suggests that under the mild conditions employed, this reaction stops after the first step of the Arbuzov mechanism, i.e. the phosphonium salt (4) appears to be stable, and breakdown occurs upon work-up. Compound (4) is stable under nitrogen, however exposure to air results in fuming and very rapid breakdown to trimethylsilyl dimethylphosphinate.

In conclusion, this Letter describes alkylation of bis(trimethylsilyl)phosphonite (which was prepared *in situ*) to give both mono- and di-alkyl phosphinic acids, using simple alkyl halides under very mild conditions. This is a useful advance over existing procedures, and should allow the synthesis of complex phosphinic acids containing additional functionality, using alkylation on phosphorus as the key step.

Typical Experimental Procedures.[11]

*1. **Mono-alkylphosphinic acids:*** Ammonium phosphinate[10] (2.5 g, 30.1 mmol) and hexamethyldisilazane

(5.1 g, 31.6 mmol) were heated together at 100-110 °C under nitrogen for 1-2 h in a 100 ml 3-neck flask fitted with a septum and a condenser. The system was cooled to 0 °C and dry dichloromethane (30 ml) was injected, followed by the alkyl halide (31.6 mmol). The reaction was stirred overnight at room temperature, filtered, and the solvent removed *in vacuo* to yield an oil. This oil was dissolved in dichloromethane (with a minimum amount of methanol to achieve desilylation and solution), filtered and the solvents removed *in vacuo* to give the phosphinic acid as an oil which was dried over P_2O_5 at 40 °C at 0.1 mmHg overnight.

2. Mono-alkyl adamantanammonium phosphinates: The procedure for the synthesis of mono-alkylphosphinic acids was followed (as above), however after removal of the solvent from the reaction, the residue was cooled to 0 °C and dissolved in tetrahydrofuran (10 ml). A solution of 1-adamantanamine (1.05 eq.) in tetrahydrofuran-methanol (3:1) (60 ml) was then added and stirred overnight. The crystalline phosphinate salt was collected by filtration, and washed with diethyl ether. Concentration of the tetrahydrofuran-methanol filtrate followed by dilution with diethyl ether and filtration generally yielded a second crop of product.

3. Di-alkylphosphinic acids: Ammonium phosphinate (2.5 g, 30.1 mmol) and hexamethyldisilazane (4.9 g, 30.1 mmol) were heated together at 100-110 °C under nitrogen for 1-2 h as above. The system was cooled to 0 °C and dry dichloromethane (30 ml) was injected, followed by the alkyl halide (30.1 mmol). The reaction was stirred overnight at room temperature, cooled to 0 °C, and hexamethyldisilazane (4.9 g, 30.1 mmol) was added. After 2 h the appropriate second electrophile was added at 0 °C, and stirred overnight at room temperature. After filtration the reaction was worked up in one of two ways: either the solvent was removed *in vacuo* to yield an oil which was dissolved in dichloromethane (with a minimum amount of methanol to achieve desilylation and solution), refiltered, and the solvents removed *in vacuo* to give the phosphinic acids, or, alternatively, the solution was washed with aqueous acid and the phosphinic acid was isolated after removal of the solvents.

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11. Satisfactory IR, NMR (^1H, ^{31}P, and ^{13}C), mass spectra and accurate mass measurements were obtained for all new compounds.

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