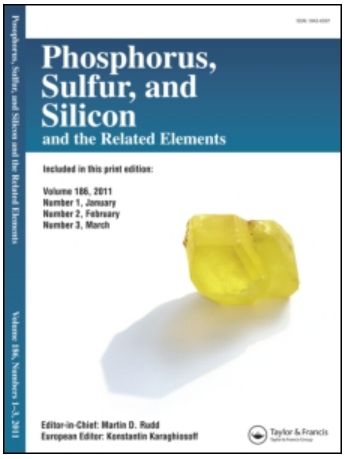

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MONO- AND DIALKYLATION OF ISOPROPYL PHOSPHINATE-A SIMPLE PREPARATION OF ALKYLPHOSPHINATE ESTERS[1]

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MONO- AND DIALKYLATION OF ISOPROPYL PHOSPHINATE—A SIMPLE PREPARATION OF ALKYLPHOSPHINATE ESTERS[1]

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Dedicated to Professor John Verkade on the occasion of his 60th birthday

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Base-catalysed alkylation of isopropyl phosphinate with primary alkyl halides under mild conditions affords the corresponding alkyl phosphinate esters in fair to excellent yields.

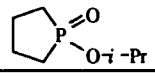
Key words: Phosphinate esters, preparation, primary halides.

INTRODUCTION

Mono and dialkyl substituted phosphinic acid derivatives (RPH(O)X and RR'P(O)X; R = alkyl or aryl, X = electronegative substituent) are very useful intermediates for the synthesis of many organophosphorus compounds but general methods for their preparation, particularly the alkyl members, are lacking.[2] Disubstituted acids (diaryl and aralkyl) have been extensively studied but monosubstituted derivatives are rare and derived largely from phosphorus halides, $RPCl_2$ or R_2PCl, and their readily accessible derivatives. These latter are themselves not easily prepared except in a few instances. A specialized approach is the addition of $H_2P(O)H$ and RPH(O)OH to aldehydes and ketones which, though general, is restricted to the generation of α-hydroxy derivatives.

A convenient starting material for the synthesis of alkyl phosphinic acids would seem to be phosphinic(hypophosphorus) acid itself, $H_2P(O)OH$, which is cheap and readily available as a high purity aqueous solution. Alkyl phosphinates, $AlkOP(O)H_2$, are accessible by azeotropic distillation of a mixture of acid, alcohol and benzene,[2b] reaction of the acid with trialkyl orthoformates[2a] and, less conveniently, by reaction of the acid with a diazoalkane.[2a] The esters undergo base catalyzed addition to Michael acceptors[3] but attempted alkylation under the same conditions of the methyl and ethyl esters was defeated by rapid decomposition of the anion.[4] A variant on this is to alkylate $(EtO)_2CHPH(O)OEt$, readily available from phosphinic acid and

TABLE I

Alkyl halide (RCH_2X)	NaO-*i*-Pr (eq)	Product	Yield (%)	^{31}P NMR δ ppm, ($^1J_{PH}$ Hz)
CH_2=$CHCH_2Br$	1	**1**.CH_2:$CHCH_2PH(O)O$-*i*-Pr	65	33.16, (532.5)
CH_3I (1 eq)	1	**2**.$CH_3PH(O)$-*i*-Pr	90	32.87(549.3)
CH_3I (2 eq)	2	**3**.$(CH_3)_2P(O)$-*i*-Pr	90	54.04
$PhCH_2Br$ (1eq)	1	**4**.$PhCH_2PH(O)O$-*i*-Pr	72	34.55, (540.3)
$PhCH_2Br$ (2eq)	2	**5**.$(PhCH_2)_2P(O)O$-*i*-Pr	95	47.47
n-Pentyl Iodide (1eq)	1	**6**.n-$C_5H_{11}PH(O)O$-*i*-Pr	73	36.73, (523.3)
$Br(CH_2)_4Br$	1	**7**.$Br(CH_2)_4HP(O)$-*i*-Pr	50	35.27, (523.0)
$Br(CH_2)_4Br$	2	**8**. 	40	78.49

an excess of triethyl orthoformate,[5] and to remove the $(EtO)_2CH$ group by acid hydrolysis. This sequence has been successfully used[6] to make a series of GABA antagonists. During the course of our work towards the synthesis of phosphosugars,[7] we have now found that, in contrast to its lower homologues, isopropyl phosphinate is sufficiently stable to be alkylated directly. Monoalkyl- and symmetrical or unsymmetrical dialkylphosphinates are easily accessible in this way.

Direct alkylation has been overlooked until now, presumably due to the ready decomposition of the esters under basic conditions. The results and the experimental conditions are described in the following equations and Table I.

RESULTS AND DISCUSSION

$$H_2P(O)OH + i\text{-}PrOH \xrightarrow[\text{reflux}]{\text{benzene}} H_2P(O)O\text{-}i\text{-}Pr$$

$$H_2P(O)O\text{-}i\text{-}Pr + RX + NaO\text{-}i\text{-}Pr\ (1\ eq) \xrightarrow[\text{RT, 30 min}]{\text{THF/}i\text{-PrOH}} RHP(O)O\text{-}i\text{-}Pr$$

$$H_2P(O)O\text{-}i\text{-}Pr + RX\ (2\ eq) + NaO\text{-}i\text{-}Pr\ (2\ eq) \xrightarrow[\text{RT, 1 h}]{\text{THF/}i\text{-PrOH}} R_2P(O)O\text{-}i\text{-}P$$

$$RHP(O)O\text{-}i\text{-}Pr + R'X + NaO\text{-}i\text{-}Pr\ (1\ eq) \xrightarrow[\text{RT, 1 h}]{\text{THF/}i\text{-PrOH}} RR'P(O)O\text{-}i\text{-}Pr$$

As shown, isopropyl phosphinate reacts with primary alkyl halides in the presence of one equivalent of base at room temperature giving monoalkylphosphinate esters exclusively; with two equivalents of base, symmetrical dialkylphosphinates are obtained and unsymmetrical examples can be prepared by sequential monoalkylations

in the same pot. At higher temperature the alkylation is not selective and gives mixtures of mono and dialkylated products.

Reaction of isopropyl benzylphosphinate **4** with methyl iodide gave isopropyl benzylmethylphosphinate **9** in 70% yield. Alkylation of **4** with allyl bromide gave isopropyl benzyl-1-propenylphosphinate **10** in 60% yield.

$$PhCH_2(H)P(O)O\text{-}i\text{-}Pr + CH_3I \xrightarrow[NaO\text{-}i\text{-}Pr]{THF/i\text{-}PrOH} \underset{\mathbf{9}}{PhCH_2(CH_3)P(O)O\text{-}i\text{-}Pr}$$

$$PhCH_2(H)P(O)O\text{-}i\text{-}Pr + BrCH_2CH{=}CH_2 \xrightarrow[NaO\text{-}i\text{-}Pr]{THF/i\text{-}PrOH} \underset{\mathbf{10}}{\begin{array}{l} PhCH_2P(O)O\text{-}i\text{-}Pr \\ | \\ CH{:}CHCH_3 \end{array}}$$

Isopropyl phosphinate was prepared conventionally by azeotropic distillation; a 50% solution in tetrahydrofuran containing 10% of isopropanol appeared indefinitely stable at 6°C. Distillation was not attempted because of the known[8] thermal instability of the esters. No phosphorus containing impurities were detectable by NMR.

There is a marked difference in rates of alkylation to give either mono or bis, at room temperature, making preparation of the mono a simple process. The base used was isopropoxide anion prepared from the alcohol and sodium hydride. This base avoids transesterification problems and is sufficiently strong to remove the proton from monosubstituted phosphinates as well, thus allowing sequential alkylations in the same pot, e.g., the preparation of **3**, **5**, and **8**. However, the base is also sufficiently strong to rearrange the allyl group to propenyl under the slightly more forcing conditions necessary for disubstitution. Thus, attempted allylation of isopropyl benzylphosphinate affords instead the benzyl(1-propenyl)phosphinate.

All attempts at using secondary halides in the alkylation were unsuccessful, the only products observed being di-isopropyl phosphonate and its anion (δ^{31}P 152.5). We attribute this to the more sluggish reaction expected with secondary halides, allowing the phosphinate anion to decompose by alternative pathways.[4] The increased stability of the isopropyl phosphinate compared with its methyl and ethyl analogues presumably is due to the reduced leaving group capacity of isopropoxide anion slowing down the decomposition of the phosphinate ester anion. Possibly, the readily accessible *t*-butyl ester[4a] would be even more stable under basic conditions but we have not explored this.

EXPERIMENTAL

^{1}H NMR (300 MHz), ^{13}C NMR (75 MHz), and ^{31}P NMR (121.508 MHz) were recorded on Bruker ACF 300, ACP 300 FT NMR spectrometers. ^{31}P NMR spectra were obtained with and without full proton decoupling and are reported in ppm relative to external 85% phosphoric acid (δ = 0). All ^{1}H NMR spectra were reported in ppm relative to tetramethylsilane, multiplicity (br, broad; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, doublet of doublets; 2d two doublets; bd broad doublet). Mass spectra were recorded on an MS-50 mass spectrometer. Melting points were determined in open capillary tube and are uncorrected. Merck (70–230 mesh) silica gel was used for column chromatography and all solvents were distilled before use. Reactions were carried out under argon and monitored by TLC and/or ^{31}P NMR. The procedure described for the preparation of isopropyl allylphosphinate (**1**) was used for all the alkylation reactions.

Isopropyl phosphinate: In a 500 mL round bottomed flask fitted with a Dean-Stark trap were placed 35 g (0.53 mol) of crystalline hypophosphorous acid (obtained from commercial 40% aqueous solution by vacuum distillation at 40° followed by freeze drying), 110 mL of isopropyl alcohol and 300 mL of benzene. The mixture was heated at reflux and water was removed until esterification was complete by ^{31}P NMR. The solution was cooled to room temperature and concentrated under vacuum. The residue was pure by ^{1}H NMR and used without further purification. The isopropyl hypophosphite was stored as 50% solution in THF containing 10% isopropyl alcohol. Yield was quantitative by nmr. ^{31}P NMR (THF) δ 9.5 (t, $^{1}J_{P\_\_H}$ = 561 Hz); ^{1}H NMR ($CDCl_3$) δ 7.18 (d, J = 560 Hz, 2H), 4.69 (m, 1H), 1.40 (d, J = 6.15 Hz, 6H).

Isopropyl allylphosphinate (**1**): To a solution of isopropyl phosphinate (10.0 g, 92.5 mmol) and allyl bromide (13.3 g, 92.5 mmol) in 200 mL of dry THF at room temperature was added a solution of sodium isopropoxide 92.5 mmol) in 100 mL of 2:1 THF:isopropanol very slowly with stirring. The mixture was stirred at room temperature under argon for 30 min. The progress of the reaction was checked by ^{31}P NMR. The solution was filtered and the filtrate was concentrated on the rotavapor. The residue was dissolved in 300 mL of ethyl acetate and washed with 0.5 M HCl, and brine solution and dried over anhydrous sodium sulfate. The removal of the solvent gave a yellow oil. This was distilled to give a clear oil. b.pt. 58–64°C (1 mmHg), Yield 55–65%. ^{31}P NMR ($CDCl_3$) δ 33.1 (d, $^{1}J_{P-H}$ = 532.5 Hz). ^{1}H NMR ($CDCl_3$) δ 6.88 (d, J = 540 Hz, 1H), 5.65–5.54 (m, 1H), 5.11 (m, 2H), 4.52 (m, 1H), 2.50 (dd, J = 7.8, 18.9 Hz, 2H), 1.24–1.18 (2d, J = 6.23 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 125.5 (d, J = 9.75 Hz), 120.75 (d, J = 13.9 Hz), 70.95 (d, J = 6.15 Hz), 34.7 (d, J = 89.6 Hz), 23.8, 23.5; GCMS m/e 149 (M + 1), 147, 133, 107 (100%), 106, 89, 69, 65, 43.

Isopropyl methylphosphinate (**2**): Yield 90%. ^{31}P NMR ($CDCl_3$) δ 32.87 ($^{1}J_{P-H}$ = 539 Hz), ^{1}H NMR ($CDCl_3$) δ 7.5 (dd, J = 2.07, 538 Hz, 1H), 4.69–4.59 (m, 1H), 1.51 (dd, J = 2.07, 15 Hz, 3H), 1.33 (dd, J = 6.15, 11.28 Hz, 6H). GCMS m/z 123 (M + 1), 121 (M − 1), 107 (M − 15), 81 (100%).

Isopropyl dimethylphosphinate (**3**): Same procedure with two equivalents of methyl iodide and two equivalents of base. Yield 90%. ^{31}P NMR ($CDCl_3$) δ 54.04. ^{1}H NMR ($CDCl_3$) δ 4.60–4.51 (m, 1H), 1.52 (d, J = 15 Hz, 6H), 1.30 (d, J = 6.15 Hz). GCMS (EI^+) m/z 137 (M + 1), 121 (M − 15), 95, 77 (100%).

Isopropyl benzylphosphinate (**4**): Yield 72%. ^{31}P NMR ($CDCl_3$) δ 34.55 (d, $^{1}J_{P-H}$ = 540.3 Hz). ^{1}H NMR ($CDCl_3$) δ 7.04 (d, J = 541 Hz, 1H), 7.33–7.19 (m, 5H), 4.61–4.52 (m, 1H), 3.18–3.12 (d, 18 Hz, 2H), 1.32 (d, J = 6.15 Hz, 3H), 1.22 (d, J = 6.15 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 131.7, 129.8, 129.7, 129.6, 128.7, 127.0, 71.5 (d, J = 8 Hz), 37.1 (d, J = 89.9 Hz), 24.03 (d, J = 4.0 Hz), 23.1 (d, J = 5.05 Hz). GCMS (EI^+) m/z 198 (M^+), 156, 139, 119, 107, 92, 91 (100%).

Isopropyl dibenzylphosphinate (**5**): Same procedure with two equivalents of benzyl bromide and two equivalents of base: white crystals, mp 81–82° (EtOAc/hexanes); yield 95%. ^{31}P NMR ($CDCl_3$) δ 47.47. ^{1}H NMR ($CDCl_3$) δ 7.32–7.23 (m, 10H), 4.51–4.45 (m, 1H), 3.08–3.00 (dd, J = 3.06, 15.9 Hz, 4H), 1.01 (d, J = 6.1 Hz, 6H). MS (EI^+) m/z 288 (M), 273, 246, 197 (M − 91), 91 (100).

Isopropyl n-pentylphosphinate (**6**): Yield 73%. B.Pt. 70–75°C (1 mm). ^{31}P NMR ($CDCl_3$) δ 36.73 (d, $^{1}J_{P-H}$ = 523 Hz). ^{1}H NMR ($CDCl_3$) δ 7.03 (d, J = 531 Hz, 1H), 4.70–4.15 (m, 1H), 1.8–1.65 (m, 2H), 1.62–1.45 (m, 2H), 1.4–1.3 (m, 10H), 0.84 (t, 3H). ^{13}C NMR ($CDCl_3$) δ 70.6 (d, J = 7.7 Hz), 32.3 (d, J = 15.1 Hz), 28.7 (d, J = 94.0 Hz), 24.1, 23.1, 21.9, 20.2, 13.6. GCMS EI^+) m/z 179 (m + 1), 163 (M − 15), 137, 80 (100%).

Isopropyl 4-bromobutylphosphinate (**7**): Yield 50%, ^{31}P NMR ($CDCl_3$) δ 35.27 (d, $^{1}J_{P-H}$ = 523 Hz). ^{1}H NMR ($CDCl_3$) δ 7.14 (d, J = 528 Hz, 1H), 4.75–4.66 (m, 1H), 3.408 (t, J = 4.29 Hz, 2H), 1.97 (m, 2H), 1.77 (m, 4H), 1.35 (d, J = 6.5 Hz, 3H), 1.32 (d, J = 6.5 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 71.2 (d, J = 6.06), 32.8, 32.6, 32.4, 28.4, 27.1, 24.0, 23.0, 19.2. GCMS (EI^+) m/z 229, 227 (M − 15), 203, 201 (M − 42), 121 (100%).

1-Oxo-1-isopropropoxy phospholane (**8**): Same procedure as for **7** but with two equivalents of base. Yield 40%, B.Pt. 70–72°C (1 mm). ^{31}P NMR ($CDCl_3$) δ 78.49. ^{1}H NMR ($CDCl_3$) δ 4.60–4.53 (m, 1H), 1.83–1.70 (m, 2H), 1.67–1.56 (m, 2H), 1.22 (d, J = 6.5 Hz, 6H). ^{13}C NMR ($CDCl_3$) δ 69.3 (d, J = 6.12 Hz), 25.7–24.5 (d, J = 90 Hz), 24.04, 22.9 (d, J = 11.6 Hz). GCMS (EI^+) m/z 147 (M − 15), 121, 104, 103.

Alkylation of isopropyl benzylphosphinate (**4**): To a solution of isopropyl benzylphosphinate **4** (0.8 g, 4.29 mmol) and alkyl halide (5 mmol) in 25 mL of dry THF containing 1 mL of dry isopropanol was added sodium isopropoxide (4.29 mmol) slowly. The reaction mixture was stirred at room temperature under argon for 1–2 hours. The progress was monitored by ^{31}P NMR. The reaction was quenched by adding water and extracted with chloroform. Evaporation of the solvent gave an oil which was purified by column chromatography.

Isopropyl benzylmethylphosphinate (**9**): Yield 70%, ^{31}P NMR ($CDCl_3$) δ 46.5. ^1H NMR ($CDCl_3$) δ 7.26–7.25 (m, 5H), 4.65–4.55 (m, 1H), 3.10 (d, J = 18 Hz, 2H), 1.40 (d, J = 15 Hz, 3H), 1.25 (d, J = 6.40, 3H), 1.20 (d, J = 6.4 Hz, 3H). MS (EI) m/z 212 (M^+), 197, 170, 154, 107, 92, 91 (100%).

Isopropyl benzyl-1-propenylphosphinate (**10**): Yield 60%, ^{31}P NMR ($CDCl_3$) δ 36.3 (s). ^1H NMR ($CDCl_3$) δ 7.28–7.19 (m, 5H), 6.8–6.5 (m, 1H), 5.56 (dd, J = 15.9, 23.0 Hz, 1H), 4.55–4.47 (m, 1H), 3.08 (dd, J = 3.71, 18 Hz, 2H), 1.83 (d, J = 6.4 Hz, 3H), 1.24 (d, J = 6.5 Hz, 3H), 1.18 (d, J = 6.5 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 148.9, 131.8, 129.8, 128.2, 126.3, 121.4 (d, J = 125.3), 69 (d, J = 8.1 Hz), 37.9 (d, J = 95 Hz), 24.2, 23.9, 19.8.

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