Direct Monoalkylation of Alkyl Phosphinates to Access H-Phosphinic Acid Esters

Isabelle Abrunhosa-Thomas, Patrice Ribière, Alicia C. Adcock, Jean-Luc Montchamp*

Department of Chemistry, Box 298860, Texas Christian University, Fort Worth, TX 76129, USA
Fax +1(817)2575851; E-mail: j.montchamp@tcu.edu

Received 1 July 2005

Abstract: Simple alkyl phosphinates prepared by the silicate esterification method can be alkylated under Barbier-like conditions with butyl lithium at −78 °C followed by warming to room temperature. The method is limited to the more reactive electrophile such as allylic bromides and alkyl iodides. With these electrophiles good yields of H-phosphinic acid esters are generally obtained in a straightforward manner.

Key words: phosphorus, H-phosphinic acid, phosphinates, alkylation, hypophosphite

In principle, the direct alkylation of alkyl phosphinates [ROP(O)H₂] under basic conditions would be an efficient approach towards variously substituted H-phosphinic acid esters [R'P(O)(OR)H]. However, this approach was not considered viable until Gallagher reported the alkylation of isopropyl phosphinate using alkyl halides and sodium isopropoxide (Equation 1).¹ Previously, only conjugate addition using a catalytic amount of base was demonstrated.² The reason for the failed alkylation was proposed to be the result of the rapid decomposition of the anion derived from unhindered esters (R = Me, Et) of hypophosphorous acid.³ Gallagher prepared isopropyl phosphinate using the Nifant’ev esterification method,⁴ and successful alkylation was attributed to the more hindered nature of the ester which slowed down decomposition.¹ Unfortunately, this method has apparently not found widespread use, in spite of the importance of H-phosphinic acid esters as intermediates for the preparation of various organophosphorus compounds. Instead the alkylation of alkyl phosphinate equivalents [(EtO)₂CHP(O)(OEt)H, and (EtO)₂CMeP(O)(OEt)H, ‘Ciba-Geigy reagents’] has been employed commonly even if it involves a protection-deprotection sequence.⁵

A few years ago, we reported a novel and high yielding method to prepare alkyl phosphinates using alkoxysilanes or silicates (Equation 2).⁶ It was found that the alkyl phosphinates are more robust than when prepared with the other methods.⁶ We therefore set out to investigate the alkylation of these phosphinates under basic conditions, and the results are presented herein.

Equation 2

Alkyl phosphinates were prepared by our silicate method⁶ (Equation 2) and used in situ, since isolation of alkyl phosphinates is not possible due to the sensitivity of these esters. We previously showed that alkyl phosphinate solutions can be used conveniently for a wide range of reactions.⁶,⁷

The alkylation of ethyl phosphinate with benzyl bromide was selected as the model reaction. Because butyl lithium is employed, we further settled on THF as the solvent. After some experimentation, it was found that Barbier-like conditions in which the base is added to a mixture of the nucleophile (alkyl phosphinate) and electrophile (alkyl halide) in nearly stoichiometric ratios, is more satisfactory and also experimentally simpler. Table 1 shows the results with various alkyl halides and phosphinates. Under these conditions, ethyl H-benzylphosphinate was obtained in 71% isolated yield (Table 1, entry 1). The alkylation of butyl and isopropyl phosphinates proceeded similarly (entries 2 and 3). Benzyl phosphinate was also benzylated successfully (entry 4) but in lower yield due to the higher hydrolytic lability of the product during chromatographic purification over silica gel.⁸ There was no significant difference between the preparation of the alkyl phosphinate from H₃PO₂ or from anilinium hypophosphite.

Reactive electrophiles generally give good yields, but less reactive halides are problematic (Table 1). 2-Bromobenzyl bromide reacted uneventfully (entry 5). Butyl iodide still delivered an acceptable yield (entries 6 and 7), except with benzyl phosphinate (entry 8). As expected, octyl iodide reacted similarly (entry 9), but the bromide was unsatisfactory (entry 10). Although this fact represents a
significant limitation, alkyl H-phosphinates can be obtained from the corresponding alkenes using methodology we have developed.\(^9\)

For benzylic substrates, we have also reported a palladium-catalyzed cross-coupling approach.\(^10\) Another approach\(^11\) involves the reaction of the Grignard reagent with \(\text{ClP(OR)}_2\) but it suffers from obvious limitations, and provides butyl benzyl-H-phosphinate in 58% yield\(^11c\) (compared to 70% in entry 2). Unfortunately, there is still no general approach to prepare alkyl H-phosphinates from alkyl halides. In our hands, even the Gallagher method\(^1\) (Equation 1) which reportedly works with a bromoalkane is unsatisfactory, and this prompted the present study.

Methylation is readily accomplished with \(\text{MeI}\). Both butyl and benzyl methyl-H-phosphinate esters are obtained in good yields (entries 11 and 12, respectively). For comparison, the Grignard method affords butyl methyl-H-phosphinate in 55% yield.\(^11c\) Methyl-H-phosphinate esters are also available from the reaction of an alcohol with commercially available dichloromethylphosphine \((\text{CH}_3\text{PCl})_2\),\(^12\) but the latter reagent is expensive and hazardous. The methylation of benzyl phosphinate produces the novel and synthetically useful intermediate which we are currently employing in a variety of synthetic applications. Scheme 1 shows an example, in connection with a project aiming at the preparation of GABA analogues. \(\text{N,O-Bis(trimethylsilyl)acetamide (BSA)}\)–promoted addition of reagent \(1\) to CBZ-protected piperidone, followed by cleavage of the resulting silyl ether,\(^13\) produced intermediate \(2\). Hydrogenolysis then cleanly delivered the pure GABA analogue \(3\) as the zwitterion, without the need for tedious ion-exchange chromatography. Analogue \(3\) showed no activity on the \(\text{GABA}_\text{A}\) receptor.\(^14\) Reagent \(1\) can be prepared routinely in multigram quantities.

---

### Table 1 Butyl Lithium Promoted Alkylation of Alkyl Phosphinates under Barbier-like Conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>(R)</th>
<th>Electrophile</th>
<th>Product</th>
<th>Isolated yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Et</td>
<td>Benzyl bromide</td>
<td><img src="benzyl_bromide" alt="image" /></td>
<td>71</td>
</tr>
<tr>
<td>2</td>
<td>Bu</td>
<td>Butyl iodide</td>
<td><img src="butyl_iodide" alt="image" /></td>
<td>70</td>
</tr>
<tr>
<td>3</td>
<td>i-Pr</td>
<td>Octyl iodide</td>
<td><img src="octyl_iodide" alt="image" /></td>
<td>65</td>
</tr>
<tr>
<td>4</td>
<td>Bn</td>
<td>Octyl bromide</td>
<td><img src="octyl_bromide" alt="image" /></td>
<td>45</td>
</tr>
<tr>
<td>5</td>
<td>Bu</td>
<td>2-Bromobenzyl bromide</td>
<td><img src="2-bromobenzyl_bromide" alt="image" /></td>
<td>76</td>
</tr>
<tr>
<td>6</td>
<td>Et</td>
<td>Butyl iodide</td>
<td><img src="butyl_iodide" alt="image" /></td>
<td>70</td>
</tr>
<tr>
<td>7</td>
<td>Bu</td>
<td>Butyl iodide</td>
<td><img src="butyl_iodide" alt="image" /></td>
<td>65</td>
</tr>
<tr>
<td>8</td>
<td>Bn</td>
<td>Butyl iodide</td>
<td><img src="butyl_iodide" alt="image" /></td>
<td>45</td>
</tr>
<tr>
<td>9</td>
<td>Bu</td>
<td>Octyl iodide</td>
<td><img src="octyl_iodide" alt="image" /></td>
<td>35</td>
</tr>
<tr>
<td>10</td>
<td>Bu</td>
<td>Octyl bromide</td>
<td><img src="octyl_bromide" alt="image" /></td>
<td>8</td>
</tr>
<tr>
<td>11</td>
<td>Bu</td>
<td>MeI</td>
<td><img src="methyl_iodide" alt="image" /></td>
<td>82</td>
</tr>
<tr>
<td>12</td>
<td>Bn</td>
<td>Bu</td>
<td><img src="butyl_bromide" alt="image" /></td>
<td>76</td>
</tr>
<tr>
<td>13</td>
<td>Bu</td>
<td>Allyl bromide</td>
<td><img src="allyl_bromide" alt="image" /></td>
<td>71</td>
</tr>
<tr>
<td>14</td>
<td>Bn</td>
<td>Allyl bromide</td>
<td><img src="allyl_bromide" alt="image" /></td>
<td>39</td>
</tr>
<tr>
<td>15</td>
<td>Bu</td>
<td>Cinnamyl chloride</td>
<td><img src="cinnamyl_chloride" alt="image" /></td>
<td>0</td>
</tr>
<tr>
<td>16</td>
<td>Bu</td>
<td>Cinnamyl bromide</td>
<td><img src="cinnamyl_bromide" alt="image" /></td>
<td>60</td>
</tr>
<tr>
<td>17</td>
<td>Bu</td>
<td>Geranyl bromide</td>
<td><img src="geranyl_bromide" alt="image" /></td>
<td>62</td>
</tr>
<tr>
<td>18</td>
<td>Bu</td>
<td>Farnesyl bromide</td>
<td><img src="farnesyl_bromide" alt="image" /></td>
<td>80</td>
</tr>
<tr>
<td>19</td>
<td>Bu</td>
<td>4-Bromo-2-methyl-2-butene</td>
<td><img src="4-bromo-2-methyl-2-butene" alt="image" /></td>
<td>81</td>
</tr>
</tbody>
</table>
give any significant amounts of products include: styrene oxide, cyclohexene oxide, ethyl iodoacetate, methylene iodide, N-bromomethylphthalimide, and octyl chloride. As suggested previously, failed alkylations can be attributed to the decomposition of the anionic intermediate which then takes place more rapidly than the intermolecular reaction with the electrophile.

During these studies, the reaction of ethyl phosphate with benzyl bromide was investigated with other bases. Somewhat surprisingly, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in acetonitrile actually promoted alkylation in moderate yield (Equation 3). Analysis of the reaction mixture obtained by mixing ethyl phosphate with DBU by $^{31}$P NMR showed a peak at $\delta = 160$ ppm (dm, $J_{P-H} = 204$ Hz). This signal could correspond to the P(III) form of ethyl phosphate hydrogen-bonded to DBU [[(EtO)P(H)OH.DBU] or to a tight ion-pair, instead of the fully deprotonated phosphate anion. Allyl bromide and methyl iodide also reacted similarly, however other electrophiles only gave traces of products irrespective of the conditions (solvent, stoichiometry, temperature). With allyl bromide, a small amount of dissubstitution was observed, but the product mixture could be obtained after a simple extractive workup (Equation 4).

![Scheme 1](synthesis.png)

Scheme 1 Synthesis of a GABA analogue using reagent 1

The present method is particularly useful to access allylic H-phosphinates from the corresponding bromides. Allylic H-phosphinates have previously been obtained by the Regan–Boyd allylation of (TMSO)$_2$P=O, but the reaction is inconvenient and often produces bis-allylated products which are difficult to separate. Esterification of the H-phosphinic acid product is also required. We have shown previously that similar products can be accessed via nickel-catalyzed cross-coupling but over-reduction can also be observed. Gallagher has reported a single example using allyl bromide and isopropyl phosphate (65% yield). In comparison, our present method is advantageous because it is experimentally simple, does not require the preparation and manipulation of isopropyl phosphate (Dean–Stark, benzene removal, and solvent exchange), can be conducted on small or large scales, and it can produce various esters (entries 13 and 14). Cinnamyl, geranyl, farnesyl, and prenyl bromides all reacted in high yield (entries 16–19). Farnesyl H-phosphinate 4 is a useful intermediate as related compounds have been prepared previously through multistep synthesis. For example (Scheme 2), conjugate addition with benzyl acryl chloride afforded compound 5, which is similar to an intermediate used in the synthesis of an inhibitor of Ras farnesyl protein transferase. Through known methods, 4 is also a precursor to the corresponding phosphonochloridate which was employed in the preparation of a farnesyl pyrophosphate analogue.

![Scheme 2](synthesis.png)

Scheme 2

As mentioned above, the method is still limited to reactive electrophiles. Alkyl bromides are not sufficiently reactive, and even simple alkyl iodides only afford moderate yields. Other electrophiles that were tested but failed to
aqueous solution in vacuo on a rotary evaporator, at r.t. for 20–30 min before reaction. Anilinium hypophosphite was prepared as previously described by us. When anhyd solvents were used, they were prepared as follows: THF was distilled under N2 from Na–benzophenone ketyl, and used immediately; anhyd MeCN was freshly distilled from CaH2. 1H NMR spectra were recorded on a Varian Mercury-300 spectrometer. Chemical shifts for 1H NMR spectra are reported (in ppm) relative to internal TMS (δ = 0.00 ppm) with CDCl3 as solvent. 13C NMR spectra were recorded on a Varian Mercury-300 spectrometer at 75 MHz. Chemical shifts for 13C NMR spectra are reported (in ppm) relative to CDCl3 (δ = 77.0 ppm). 31P NMR spectra were recorded at 121 MHz on a Varian Mercury-300 spectrometer and/or at 36 MHz on an Anasazi EFT-90 spectrometer, and chemical shifts are reported (in ppm) relative to external 85% phosphoric acid (δ = 0.00 ppm). Radial chromatography was carried out with a Harrison Associates Chromatotron using 1, 2, or 4 mm layers of silica gel 60 PF 254 containing gyspum (E. Merck). Silica gel (200–300 mesh, Natland International Corporation) was used for flash chromatography. EtOAc–hexanes mixtures were used as the eluent for chromatographic purifications. TLC plates were visualized by immersion in anisaldehyde stain (by volume: 93% EtOH, 3.5% H2SO4, 1% HOAc, and 2.5% anisaldehyde) followed by heating. Mass spectrometry was provided by the Mass Spectrometry Facility of the University of South Carolina.

Formation of AlkOP(O)H2; Typical Procedure

This synthesis was conducted as described in the literature.6 A solution (or suspension) of the hypophosphorous compound (5 mmol), 4 mm layers of silica gel 60 PF 254 containing gyspum (E. Merck), 1H NMR (121.47 MHz, CDCl3): δ = 1.56 (d, JPh = 3 Hz, 3 H), 5.02, 5.10 (ABX system, JAB = 11.7 Hz, JABX = 10.5 Hz, JAX = 8.5 Hz, 2 H), 7.26 (d, JPhC = 542 Hz, 1 H). J12-7-46 (m, 6 H). 13C (1H) NMR (75.45 MHz, CDCl3): δ = 15.4 (d, JPhC = 95 Hz), 67.8 (d, JPhC = 6 Hz), 128.4, 128.9, 129.0, 135.8 (d, JPhC = 6 Hz). 31P NMR (121.47 MHz, CDCl3): δ = 35.2 (d, JPC = 542 Hz). HRMS (EI?): m/z calc'd for C20H14O2P: 328.0755; found: 328.0782.

Benzyl (N-Benzylxoxy carbonyl-4-piperidinyl)methylphosphinate 2 (Scheme 1)

To a mixture of benzyl methyl-H-phosphinate (0.198 g, 1.3 equiv, 1.2 mmol) and N-benzylxoxy carbonylpiperidin-4-one (0.23 g, 1 equiv, 0.89 mmol), in anhyd MeCN (3 mL) was added BSA (0.246 mL, 1 equiv, 0.89 mmol) dropwise at r.t. The reaction mixture was refluxed for 1.5 h, then cooled to r.t. Et3N–3 HF (0.064 mL, 0.4 equiv, 0.4 mmol) was added dropwise and the reaction mixture was warmed at 35–40 °C for 18 h. The reaction mixture was quenched with sat. aq NaHCO3 (5 mL), then washed with aq HCl (0.1 M, 5 mL), and extracted with CH2Cl2 (2 ×). The combined organic layers were washed with brine, then dried over MgSO4 and concentrated under vacuum. The resulting oil was purified by chromatography overall silica gel (hexanes–EtOAc, 60:40) to produce the expected compound (0.22 g, 60%) as a viscous yellow oil.

1H NMR (300 MHz, CDCl3): δ = 1.42 (t, JPhB = 13.2 Hz, 3 H), 1.52–1.87 (m, 4 H), 3.12–3.38 (m, 2 H), 3.95–4.19 (m, 2 H), 5.06–5.12 (m, 4 H), 7.30–7.41 (m, 10 H). 13C (1H) NMR (22.63 MHz, CDCl3): δ = 7.20–7.40 (m, 5 H). JPC = 99 Hz, 130.0782. 31P NMR (121.47 MHz, CDCl3): δ = 56.04 (81%), 54.81 (19%). HRMS (EI?): m/z calc'd for C21H20O5P: 404.1627; found: 404.1639.

(4-Hydroxy piperidin-4-yl)methyl phosphinic Acid (3) (Scheme 1)

To a dry flask under N2 containing Pd/C (10%, 0.110 mg) was added 1.5 mL of a mixture of solvent H2O–THF (1:2), following by a solution of the benzyl (N-benzylx oxy carbonyl-4-piperidinyl)methylphosphinate (0.197 g) in 3.5 mL of the same mixture of solvent H2O–THF. Then reaction was shaken in a Parr apparatus, at r.t. under H2 pressure (52 psi) for 15 h. The mixture was filtered through celite and the aqueous layer was concentrated under vacuum to give a white solid (85 mg, 100%). 1H NMR (300 MHz, CDCl3); δ = 1.24 (d, JPhB = 13.2 Hz, 3 H), 1.60–2.13 (m, 4 H), 3.22–3.37 (m, 4 H). 13C (1H) NMR (22.63 MHz, CDCl3); δ = 9.81 (d, JPhB = 92 Hz), 26.9 (d, JPhC = 5.2 Hz), 38.6 (d, JPhC = 8.8 Hz), 67.7 (d, JPhC = 116 Hz). 31P NMR (121.47 MHz, CDCl3); δ = 43.48.

HRMS (EI?): m/z calc'd for C23H30O5PN: 408.1078; found: 408.1078.

Ethyl Benzyl-H-phosphinate22 (Equation 3)

To a mixture of benzyl bromide (0.94 g, 1.1 equiv, 5.5 mmol) and a solution of EtOP(O)H2 (10 mL, 0.5 M in MeCN, 1 equiv, 5 mmol) in a dry flask under N2, was added DBU (0.84 g, 1.1 equiv, 5.5 mmol) at r.t. A water bath was used to prevent any increase in the temperature. After 1 h, the mixture was quenched with a 10% NaHCO3 solution (5 mL) and extracted with EtOAc. The combined organic phases were washed with brine, then dried over MgSO4. Concentration afforded the crude compound, which was purified by silica gel chromatography (hexanes → EtOAc) to produce the expected compound (0.50 g, 54%) as a clear oil. Yield: 71%; RN: [114425-49-9]. 1H NMR (300 MHz, CDCl3): δ = 1.31 (t, J = 7 Hz, 3 H), 3.20 (dd, JPhB = 18 Hz, J = 2 Hz, 2 H), 3.95–4.20 (m, 2 H), 7.05 (dt, JPhB = 544 Hz, J = 2 Hz, 1 H), 7.20–7.40 (m, 5 H). 13C (1H) NMR (75.45 MHz, CDCl3): δ = 16.2 (d, JPhC = 6 Hz), 37.0 (d, JPhC = 89 Hz), 62.7 (d, JPhC = 7 Hz), 127.2 (d, JPhC = 4 Hz), 128.9 (d, JPhC = 3 Hz), 129.7 (d, JPhC = 6 Hz), 129.8 (d, JPhC = 7 Hz).
The combined organic phases were washed with brine, and dried with a 10% aq NaHSO₄ solution (5 mL) and extracted with EtOAc. After 1 h, the mixture was washed with hexanes (3×) and re-extracted with EtOAc. The combined organic phases were washed with brine, and dried over MgSO₄. Concentration afforded cleanly a mixture of the mono-alkylation and bis-alkylation products as a clear oil (0.35 g, 84%, 8:1 ratio).

Mono-Alkylation Product
Yield: 76%; RN: [115049-29-1].

1H NMR (300 MHz, CDCl₃): δ = 1.37 (t, J = 7 Hz, 3 H), 2.67 (dd, J = 8, 19 Hz, 2 H), 4.1–4.5 (m, 2 H), 5.3–5.4 (m, 2 H), 5.65–5.85 (m, 1 H), 7.02 (dt, J=454 Hz, J = 1.8 Hz, 1 H), 7.21–7.37 (m, 5 H).

13C {1H} NMR (75.45 MHz, CDCl₃): 21.8 (d, J=35.1 Hz, CH₂), 23.8 (d, J=40.7 Hz, CH₂), 65.9 (d, J=32.2 Hz, CH₃), 66.8 (d, J=32.2 Hz, CH₃). 

31P NMR (121.47 MHz, CDCl₃): δ = 37.26 (dm, J=544 Hz, 1 H). HRMS (EI+): m/z calcd for C₁₁H₁₉O₂PBr: 291.0150; found: 291.0153.

Ethyl Butyl-H-phosphinate¹⁻²⁰ (Table 1, Entry 6)
Yield: 7%; RN: [21661-55-2].

1H NMR (300 MHz, CDCl₃): δ = 0.91–0.97 (m, 2 H), 7.08 (d, J=629 Hz, 1 H).

13C (¹H) NMR (75.45 MHz, CDCl₃): δ = 13.8, 18.9, 22.9 (d, J=3.2 Hz), 23.8 (d, J=16 Hz), 26.8 (d, J=9 Hz, 32, 32.6 (d, J=6 Hz, 62.5 (d, J=6 Hz). 9). 

31P NMR (121.47 MHz, CDCl₃): δ = 0.32 (dm, J=544 Hz). HRMS (EI+): m/z calcd for C₉H₁₃O₂BrP: 217.1201; found: 217.1201.

Butyl Octyl-H-phosphinate⁹ (Table 1, Entry 9)
Yield: 51%; RN: [21661-55-2].

1H NMR (300 MHz, CDCl₃): δ = 0.91–0.97 (m, 2 H), 7.08 (d, J=629 Hz, 1 H).

13C (¹H) NMR (75.45 MHz, CDCl₃): δ = 13.8, 18.9, 22.9 (d, J=3.2 Hz), 23.8 (d, J=16 Hz), 26.8 (d, J=9 Hz, 32, 32.6 (d, J=6 Hz, 62.5 (d, J=6 Hz). 9). 

31P NMR (121.47 MHz, CDCl₃): δ = 0.32 (dm, J=544 Hz). HRMS (EI+): m/z calcd for C₉H₁₃O₂BrP: 217.1201; found: 217.1201.

Butyl Allyl-H-phosphinate⁶⁻²⁵ (Table 1, Entry 4)
Yield: 45%; RN: [115049-29-1].

1H NMR (300 MHz, CDCl₃): δ = 1.24, 1.33 (2× d, J = 6.2 Hz, 6 H), 3.20 (dd, J=179 Hz, J = 1.8 Hz, 2 H), 4.55–4.63 (m, 1 H), 7.06 (dt, J=454 Hz, J = 1.8 Hz, 1 H), 7.23–7.35 (m, 5 H).

13C {1H} NMR (75.45 MHz, CDCl₃): 21.8 (d, J=35.1 Hz, CH₂), 23.8 (d, J=40.7 Hz, CH₂), 65.9 (d, J=32.2 Hz, CH₃), 66.8 (d, J=32.2 Hz, CH₃). 

31P NMR (121.47 MHz, CDCl₃): δ = 35.10 (dm, J=544 Hz). HRMS (EI+): m/z calcd for C₁₀H₁₅O₂P: 212.0966; found: 212.0966.

Isopropyl Benzyl-H-phosphinate¹ (Table 1, Entry 3)
Yield: 65%.

1H NMR (300 MHz, CDCl₃): δ = 1.24, 1.33 (2× d, J = 6.2 Hz, 6 H), 3.20 (dd, J=179 Hz, J = 1.8 Hz, 2 H), 4.55–4.63 (m, 1 H), 7.06 (dt, J=454 Hz, J = 1.8 Hz, 1 H), 7.23–7.35 (m, 5 H).

13C {1H} NMR (75.45 MHz, CDCl₃): 21.8 (d, J=35.1 Hz, CH₂), 23.8 (d, J=40.7 Hz, CH₂), 65.9 (d, J=32.2 Hz, CH₃), 66.8 (d, J=32.2 Hz, CH₃). 

31P NMR (121.47 MHz, CDCl₃): δ = 35.10 (dm, J=544 Hz). HRMS (EI+): m/z calcd for C₁₀H₁₅O₂P: 212.0966; found: 212.0816; 

Benzyl Benzyl-H-phosphinate (Table 1, Entry 4)
Yield: 45%.

1H NMR (300 MHz, CDCl₃): δ = 3.24 (dd, J=19 Hz, J = 1.5 Hz, 2 H), 5.01, 5.12 (ABX system, J=11.8 Hz, J₉ₓ = 10.2 Hz, J₉ₓ = 8.5 Hz, 2 H), 7.09 (dt, J=548 Hz, J = 1.5 Hz, 1 H), 7.21–7.39 (m, 10 H).

13C (¹H) NMR (75.45 MHz, CDCl₃): δ = 37.2 (d, J=88 Hz), 68.1 (d, J=66 Hz), 127.2, 127.6 (d, J=32.2 Hz), 128.8, 128.9, 129.2 (d, J=32.2 Hz), 130.0 (d, J=66 Hz), 130.1 (d, J=7.2 Hz).

31P NMR (121.47 MHz, CDCl₃): δ = 37.73 (dm, J=544 Hz). HRMS (EI+): m/z calcd for C₁₁H₂₁O₃P: 235.1827; found: 235.1829.

Benzyl Allyl-H-phosphinate²² (Table 1, Entry 11)
Yield: 82%; RN: [6172-80-1].

1H NMR (300 MHz, CDCl₃): δ = 0.95 (t, J = 7.6 Hz, 3 H), 1.42 (sex, J = 7.6 Hz, 2 H), 1.64–1.74 (m, 2 H), 2.66 (d, J=19 Hz, J = 1.7, 7.5 Hz, 2 H), 4.03, 4.13 (t, J=6.7 Hz, J = 8.5, 9.5 Hz, J=19 Hz).
2 H), 5.25–5.82 (m, 2 H), 5.68–5.82 (m, 1 H), 7.00 (td, \( J_{HP} = 543 \) Hz, \( J = 2 \) Hz, 1 H).

1\(^{13}\)C \({ }^{1}H\) NMR (75.45 MHz, CDCl\(_3\)): \( \delta = 13.8, 18.9, 32.6 \) (d, \( J_{POCC} = 5.8 \) Hz), 35.0 (d, \( J_{POC} = 90.4 \) Hz), 66.5 (d, \( J_{POC} = 7.5 \) Hz), 121.5 (d, \( J_{POCC} = 13.8 \) Hz), 125.9 (d, \( J_{POCC} = 9.2 \) Hz).

1\(^{31}\)P NMR (121.47 MHz, CDCl\(_3\)): \( \delta = 37.69 \) (d, \( J_{PH} = 543 \) Hz).

HRMS (EI\(^{+}\)): \( m/z \) calcd for C\(_{13}\)H\(_{19}\)O\(_2\)P: 238.1123; found: 238.1122.

Butyl Farnesyl-H-phosphinate (4) (Scheme 2, Table 1, Entry 18)

Yield: 80%.

1\(^{31}\)P NMR (300 MHz, CDCl\(_3\)): \( \delta = 39.0 \) (d, \( J_{PH} = 543 \) Hz).

HRMS (EI\(^{+}\)): \( m/z \) calcd for C\(_{14}\)H\(_{27}\)O\(_2\)P: 258.1749; found: 258.1747.

Butyl Allyl-H-phosphinate (Table 1, Entry 14)

Yield: 39%.

1\(^{31}\)P NMR (300 MHz, CDCl\(_3\)): \( \delta = 2.66 \) (dd, \( J_{HP} = 18 \) Hz, \( J = 7.3 \) Hz, 2 H), 5.03, 5.15 (ABX system, \( J_{ABX} = 11.7 \) Hz, \( J_{AX} = 9.4 \) Hz, \( J_{AX} = 10.3 \) Hz, 2 H), 5.20–5.33 (m, 1 H), 1.56–5.81 (m, 2 H), 7.04 (dtd, \( J_{HP} = 549 \) Hz, \( J = 0.9, 2.3 \) Hz, 1 H), 7.34–7.51 (m, 5 H).

1\(^{1}H\) NMR (300 MHz, CDCl\(_3\)): \( \delta = 1.53–2.11 \) (m, 10 H), 2.49–2.71 (m, 4 H), 3.93–4.03 (m, 2 H), 5.05–5.11 (m, 2 H), 5.12 (s, 2 H), 5.13–5.23 (m, 1 H), 7.13–7.47 (m, 4 H).

3\(^{13}\)C \({ }^{1}H\) NMR (75.45 MHz, CDCl\(_3\)): \( \delta = 13.3, 15.7, 16.2 \) (d, \( J_{POCC} = 5.7 \) Hz), 34.3 (d, \( J_{POC} = 90.4 \) Hz), 66.6 (d, \( J_{POC} = 7.5 \) Hz), 116.9 (d, \( J_{POCC} = 10.1 \) Hz), 126.5 (d, \( J_{POCC} = 2.3 \) Hz), 128.1, 128.8, 136.1 (d, \( J_{POCC} = 4.3 \) Hz), 136.6 (d, \( J_{POCC} = 14.4 \) Hz).

1\(^{31}\)P NMR (121.47 MHz, CDCl\(_3\)): \( \delta = 37.38 \) (d, \( J_{PH} = 543 \) Hz).

HRMS (EI\(^{+}\)): \( m/z \) calcd for C\(_{10}\)H\(_{18}\)O\(_2\)P: 196.0653; found: 196.0654.

Butyl Cinnamyl-H-phosphinate (Table 1, Entry 16)

Yield: 60%.

1\(^{31}\)P NMR (300 MHz, CDCl\(_3\)): \( \delta = 0.93 \) (t, \( J = 7.6 \) Hz, 3 H), 1.42 (sext, \( J = 7.6 \) Hz, 2 H), 1.65–1.74 (m, 2 H), 2.66 (dtd, \( J = 7.6 \) Hz, \( J_{PH} = 19 \) Hz, 2 H), 4.03, 4.13 (tdd, \( J_{HP} = 6.5 \) Hz, \( J = 8.5, 10.2 \) Hz, 2 H), 6.03–6.16 (m, 1 H), 6.54 (dtd, \( J = 5.9, 15.8 \) Hz, 1 H), 7.04 (td, \( J_{PH} = 543 \) Hz, \( J = 1.7, 1.1 \) Hz), 7.27–7.37 (m, 5 H).

1\(^{1}H\) NMR (300 MHz, CDCl\(_3\)): \( \delta = 1.42 \) (sext, \( J = 7.6 \) Hz, 2 H), 1.59 (s, 2 H), 1.63–1.75 (m, 9 H), 2.08 (s, 3 H), 2.55–2.66 (m, 2 H), 3.98, 4.10 (tdd, \( J_{HP} = 6.7 \) Hz, \( J = 8.5, 10.0 \) Hz, 2 H), 5.04–5.15 (m, 2 H), 7.04 (ddd, \( J_{HP} = 537 \) Hz, \( J = 2.6 \) Hz, \( J = 1.5 \) Hz, 1 H).

1\(^{13}\)C \({ }^{1}H\) NMR (75.45 MHz, CDCl\(_3\)): \( \delta = 13.8, 16.7 \) (d, \( J_{POCC} = 3.2 \) Hz), 17.9, 19.0, 25.9, 26.6 (d, \( J_{POCC} = 3.7 \) Hz), 30.2 (d, \( J_{POC} = 94 \) Hz), 32.6 (d, \( J_{POCC} = 6 \) Hz), 39.9 (d, \( J_{POCC} = 3.5 \) Hz), 66.6 (d, \( J_{POC} = 7.2 \) Hz), 110.6 (d, \( J_{POC} = 8.9 \) Hz), 123.9, 132.0, 142.2 (d, \( J_{POCC} = 14.1 \) Hz).

1\(^{31}\)P NMR (121.47 MHz, CDCl\(_3\)): \( \delta = 38.4 \) (d, \( J_{PH} = 537 \) Hz).

HRMS (EI\(^{+}\)): \( m/z \) calcd for C\(_{13}\)H\(_{15}\)O\(_2\)P: 190.1123; found: 190.1127.

Acknowledgment

The National Institute of General Medical Sciences/NIH (1R01 GM067610) is gratefully acknowledged for financial support.

References

(2) Gallagher, M. J.; Sussman, J. Phosphorus 1975, **5**, 91.


(8) The purification of H-phosphinate esters is often complicated by the very polar nature of these compounds, and their relative ease of hydrolysis. Benzyl alkyl-H-phosphinate esters are more labile than other alkyl esters.


(14) We thank Jakob Heid, Klemens Kaupmann, and Wolfgang Froestl (Novartis Pharma) for conducting the GTPgαMS binding assay.


(19) Based on this NMR data, it is not possible to unambiguously distinguish between the anion and the proposed hydrogen-bonded or tight ion-pair structures [for example for phosphites, (RO)₃P and (RO)₂PO⁻ appear in the same range of chemical shift (δ = 130–150 ppm in ¹H NMR), though there too ion-pairs are possible]: (a) Galkin, V. I.; Khabibullina, A. B.; Smirnov, V. N.; Cherkasov, R. A.; Podovik, A. N. Dokl. Chem. (Engl. Transl.) 1987, 292, 21. (b) Moedritzer, K. J. Inorg. Nucl. Chem. 1961, 22, 19.

However, it is not likely that DBU is sufficiently basic to deprotonate the alkyl phosphate. Related P(III) compounds have been characterized, for example:


