

REPORT

INORGANIC CHEMISTRY

Phosphoric acid as a precursor to chemicals traditionally synthesized from white phosphorus

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White phosphorus, generated in the legacy thermal process for phosphate rock upgrading, has long been the key industrial intermediate for the synthesis of phosphorus-containing chemicals, including herbicides, flame-retardants, catalyst ligands, battery electrolytes, pharmaceuticals, and detergents. In contrast, phosphate fertilizers are made on a much larger scale from phosphoric acid, obtained by treating phosphate rock with sulfuric acid. Dehydration of phosphoric acid using sodium chloride gives trimetaphosphate, and here we report that trichlorosilane, primarily used for the production of high-purity silicon, reduces trimetaphosphate to the previously unknown bis(trichlorosilyl)phosphide anion. This anion offers an entry point to value-added organophosphorus chemicals such as primary and secondary alkyl phosphines, and thus to organophosphinates, and can also be used to prepare phosphine gas and the hexafluorophosphate anion, all previously available only downstream from white phosphorus.

Present industrial practice for production of most phosphorus-containing chemicals relies on energy-intensive reduction of phosphate to white phosphorus (termed the “thermal process”), followed by oxidation with hazardous chlorine to generate phosphorus trichloride (*1*). This route is followed even for mass-produced compounds, such as the herbicide glyphosate and the battery electrolyte lithium hexafluorophosphate, that in the end contain no chlorine (*2, 3*). Chemists have sought alternative, more direct reactions to transform elemental phosphorus into valuable compounds featuring phosphorus-carbon bonds, thereby omitting chlorine from the sequence (*4, 5*). A paradigm shift would be to obtain value-added phosphorus chemicals in a manner that bypasses both elemental phosphorus and chlorine with substantial reduction of energy inputs, waste, and potential for harm to the environment. Here, we describe a process that bypasses elemental phosphorus and borrows from the semiconductor industry for its energy inputs in the form of trichlorosilane, a high production-volume chemical made using HCl (*6*), that is the precursor to high-purity elemental silicon for the manufacture of solar panels (*7*).

Global production of white phosphorus (P_4) is near 1 Mt per year, with most production taking place in China and to a much lesser degree in Vietnam and Kazakhstan; production in the United States is limited to one plant, and the European Union has no capacity for production, relying entirely on imports (*8, 9*). In 2017, the EU added P_4 to its list of critical materials (*10*). Worldwide,

a shift has taken place to manufacture of high-purity phosphoric acid via phosphate treatment with sulfuric acid (termed the “wet process”) due to lower production costs and the appealing elimination of hazardous waste disposal issues connected with P_4 production (*11*). Like elemental chlorine, P_4 has been used for chemical warfare, and it is also toxic and pyrophoric (*12*). Because the wet process accounts for ~95% of all phosphate rock processed (*1*), a shift to wet-process phosphate as the starting point for production of nonfertilizer phosphorus chemicals would benefit from the economics of scale (Fig. 1). The foregoing considerations give substantial impetus for finding synthetic routes that use wet-process phosphate,

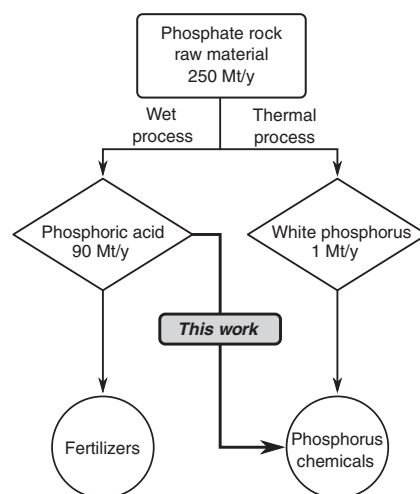


Fig. 1. Production routes to commercial phosphorus compounds from mineral sources.

instead of P_4 , as the starting point for making value-added phosphorus chemicals.

Phosphate rock used for fertilizer production, underpinning global agriculture, is initially converted into phosphoric acid by the wet process (*11*). It was shown recently that phosphoric acid can be dehydrated conveniently by reaction with sodium chloride at elevated temperatures to provide sodium trimetaphosphate (*13*). We targeted trimetaphosphate, $[P_3O_9]^{3-}$, for direct conversion to value-added chemicals, positing an analogy between the monomeric unit, metaphosphate ion (PO_3^-), and carbon dioxide. Both are Lewis acids that may act as oxide ion acceptors to provide phosphate and carbonate, respectively (*14*). We hypothesized that the Lewis acidic character of metaphosphate vis-à-vis phosphate would make this form of the raw material more prone to favorable kinetics for a reductive process.

We began our investigations by converting the sodium salt of trimetaphosphate to the tetrabutylammonium (TBA) salt, $[TBA]_3[P_3O_9] \cdot 2H_2O$, (*15*) a variant more compatible with homogeneous reaction conditions in organic solvent and analysis of products by common laboratory characterization techniques such as nuclear magnetic resonance (NMR) spectroscopy. Upon heating $[TBA]_3[P_3O_9] \cdot 2H_2O$ in neat trichlorosilane (selected because of its known ability to reduce phosphine oxides (*16*) and used here in an unoptimized 33:1 Si/P molar ratio, the excess being potentially recyclable), ^{31}P NMR spectroscopy indicated clean conversion to one new phosphorus-containing product that was identified as the bis(trichlorosilyl)phosphide anion (**1**) (Fig. 2). Anion **1** gives rise to a diagnostic ^{31}P NMR singlet at -171.7 parts per million, displaying ^{29}Si satellites ($^1J_{P-Si} = 150$ Hz) (Fig. 3A). Optimization of the reaction conditions by using a steel pressure reactor heated to $110^\circ C$ for 72 hours provided $[TBA][\mathbf{1}]$ in 65% yield on a gram scale. The identity of $[TBA][\mathbf{1}]$ was confirmed by multinuclear NMR spectroscopy, x-ray crystallography (Fig. 3B), and elemental analysis. Anion **1** is also unambiguously observable by negative-mode electrospray ionization mass spectrometry and has a characteristic isotope pattern with an average mass/charge ratio of 299.86 (fig. S45).

Recently, the carbon (*17*) and silicon (*18*) analogs of anion **1** were also successfully synthesized, suggesting a general stability of trichlorosilyl stabilized p-block anions. As the only phosphorus-containing species observable by ^{31}P NMR spectroscopy in the crude reaction mixture, **1** appears to be a stable thermodynamic sink for phosphorus under these reaction conditions. The stability of **1** is presumably a result of the electron-withdrawing trichlorosilyl groups. The phosphorus-silicon bonds are notably short at 2.128(5) Å (the sum of the single bond covalent radii is 2.27 Å) (*19*), a distance contraction indicative of delocalization of phosphorus electron density into the six $\sigma^*(Si-Cl)$ bonds. This bonding paradigm is supported by natural bond orbital (NBO) and natural resonance theory (NRT) calculations (*20*) revealing that multiple resonance structures are needed to describe the total electron density of

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1 (table S5). The chemical bonding in anion **1** is visually summarized by an electron localization function (ELF) (27) isosurface plot (Fig. 3C), where elongations of ELF P–Si bonding basins above and below the Si–P–Si plane are indicative of phosphorus-silicon multiple bonding. The packing of [TBA][**1**] in the solid state, as determined by an x-ray diffraction study, shows that the shortest contacts between the bis(trichlorosilyl)phosphide anion and the TBA cation are between the chlorine and hydrogen centers, respectively (2.78 to 2.94 Å). The phosphorus center, although it carries the formal negative charge, has longer contact distances to the TBA cation (≥ 3.07 Å).

With [TBA][**1**] in hand, we were eager to see if this salt could be used to make phosphorus-carbon bonds. An alkyl halide, (4-chlorobutyl)benzene [Ph(CH₂)₄Cl], was selected as the reaction partner to target organophosphorus products of low volatility and of relevance to the pharmaceutical industry (22). Treatment of [TBA][**1**] with Ph(CH₂)₄Cl (5 equivalents) in toluene gave the corresponding dialkylsilylphosphine [Ph(CH₂)₄]₂PSiCl₃, which was not isolated but rather converted during workup to the borane-protected secondary phosphine [Ph(CH₂)₄]₂P(BH₃)H using a solution of THF·BH₃ followed by treatment with a solution of aqueous sodium hydroxide. Before the workup procedure, silicon tetrachloride was detected as a by-product in the crude reaction mixture using ²⁹Si NMR spectroscopy. Air-stable phosphine-borane adduct [Ph(CH₂)₄]₂P(BH₃)H could be purified by column chromatography and isolated in 19% yield (unoptimized).

Conditions selective for monoalkylation of anion **1** were discovered when a preparation of the same secondary phosphine was attempted in a one-pot procedure. Accordingly, heating a mixture of [TBA]₃[P₃O₉]·2H₂O, Ph(CH₂)₄Cl and trichlorosilane was found to yield clean alkylsilylphosphine Ph(CH₂)₄P(SiCl₃)H, which was identified by ³¹P NMR spectroscopy. Cleavage of the phosphorus-silicon bond using either water or basic alumina gave the corresponding primary phosphine, Ph(CH₂)₄PH₂, which was purified by distillation and isolated in 64% yield. Anion **1** was implicated as a likely intermediate in this one-pot procedure because the same primary phosphine was also obtained when pure [TBA][**1**] was used as the phosphorus-containing starting material under otherwise identical conditions. The presence or absence of trichlorosilane in alkylation reactions of **1** therefore provides tunably selective conditions for the preparation of primary and secondary phosphines, respectively. Existing routes from primary and secondary phosphines to several important classes of phosphorus-containing compounds such as phosphonates (23) and trialkylphosphines (24) are already well established. Secondary phosphines in particular are valuable starting materials for hydrophosphination reactions (25, 26).

With (4-phenylbutyl)phosphine in hand as the product of a one-pot procedure from trimetaphosphate, we pursued a formal synthesis of fosinopril—an angiotensin-converting enzyme inhibitor used against hypertension and chronic

heart failure—by oxidizing the primary phosphine to (4-phenylbutyl)phosphinic acid. This was accomplished with excellent selectivity upon treatment with hydrogen peroxide along the lines of a literature procedure (Fig. 4) (27). The resulting (4-phenylbutyl)phosphinic acid may be converted to the target prodrug fosinopril, as reported by a group at Bristol-Myers Squibb (22). Using their synthetic scheme, the key phosphorus-carbon bond-forming step involving radical addition of hypophosphorous acid was not entirely selective for addition to the terminal, olefinic carbon of 3-

buten-1-yl-benzene. Chromatographic purification was necessary to assess the impact of regioisomeric impurities on the quality of intermediates downstream. In the case of the new phosphorus-carbon bond-forming methodology reported here (Fig. 2), in which an alkyl chloride was used as the source of the 4-phenylbutyl group in the (4-phenylbutyl)phosphinic acid synthesized, no such regioisomeric impurities are produced as side products. This example illustrates how the P-C bond-forming methodology, proceeding by way of in situ-generated bis(trichlorosilyl)phosphide,

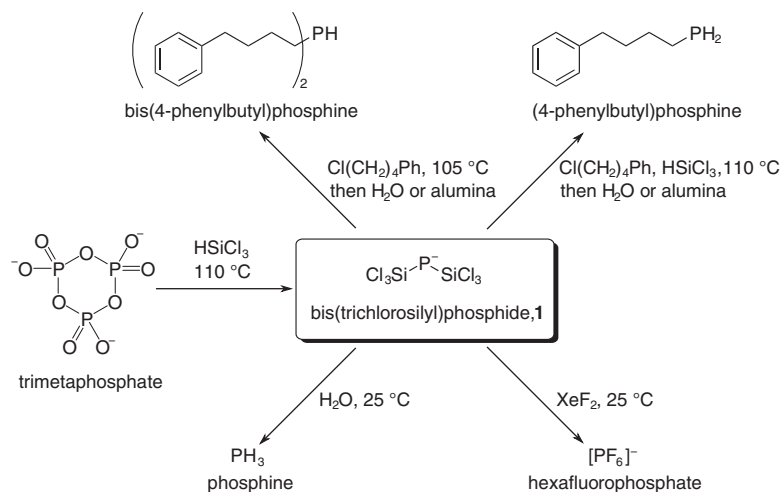


Fig. 2. Formation of bis(trichlorosilyl)phosphide (1) from trimetaphosphate and its subsequent reactivity. Compounds with phosphorus bonds to carbon, hydrogen, and fluorine are accessible.

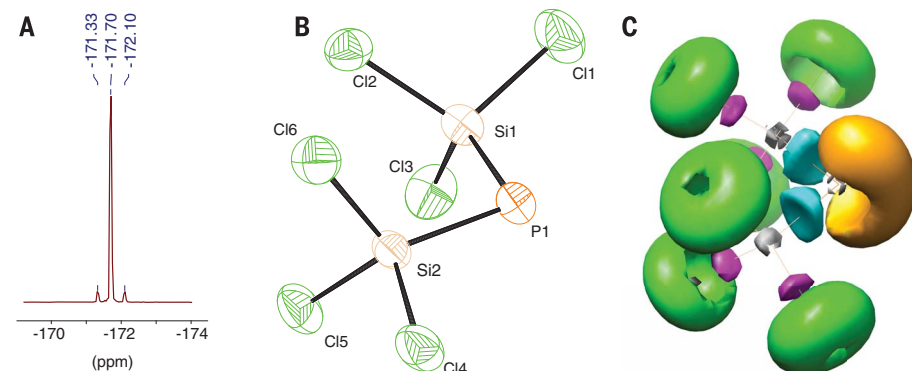


Fig. 3. Characterization of phosphide 1. (A) ³¹P NMR spectrum of [TBA][**1**] displaying ²⁹Si satellites. (B) Crystallographic structure of **1** with thermal ellipsoids shown at the 50% probability level and the TBA cation omitted for clarity. Selected bond and angle metrics: P1–Si1: 2.141(2) Å, P1–Si2: 2.1439(19) Å, Si1–P1–Si2: 97.86(8)°. (C) Plot of the 0.83 ELF isosurface. Color key: orange, P lone pair basin; cyan, P–Si bond basins; magenta, Si–Cl bond basins; and green, Cl lone pair basins.

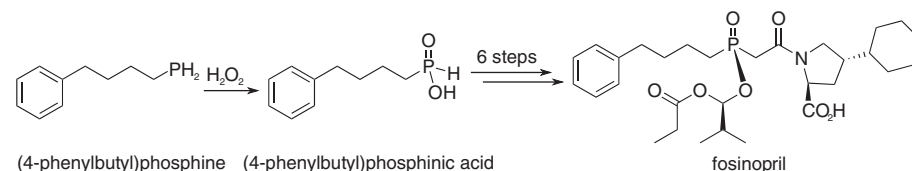


Fig. 4. Further synthetic application. Conversion of (4-phenylbutyl)phosphine to (4-phenylbutyl)phosphinic acid, an intermediate in the reported synthesis of fosinopril (22).

can be plugged into existing synthetic pathways to value-added phosphorus chemicals.

After observing hydrolytic cleavage of phosphorus-silicon bonds, we wondered whether anion **1** might react in a similar manner to produce phosphine (PH₃) (Fig. 2), which is primarily used in the fumigation industry and is typically produced by hydrolysis of metal phosphides (28). Treatment of a dichloromethane solution of [TBA][**1**] with water (15 equivalents) gave clean formation of PH₃ in at least 65% yield, as determined by quantitative ³¹P NMR spectroscopy. This reactivity is reminiscent of that reported for trisilylphosphines, such as P(SiMe₃)₃, which also react with water to give phosphine, indicative of a highly reduced phosphorus center (29). Such compounds, traditionally synthesized from white phosphorus, are used as versatile reagents for the synthesis of metal phosphides (30) and quantum dots (31).

Having established the reduced nature of the phosphorus atom in **1**, we sought to determine whether oxidation of the phosphorus-silicon bonds with a source of fluorine might give the hexafluorophosphate anion, which is extensively employed as an electrolyte component in lithium ion batteries (2). Treatment of [TBA][**1**] with xenon difluoride, a convenient laboratory source of elemental fluorine (32), gave clean conversion to the hexafluorophosphate anion as assayed by its characteristic ¹⁹F and ³¹P NMR multiplets; the hexafluorophosphate could be isolated as its lithium salt after precipitation with lithium tetrakis(pentafluorophenyl)borate ethyl etherate (Fig. 2) in 70% yield.

In the past, when high-purity phosphoric acid for the detergent industry was manufactured from white phosphorus, the latter was a linchpin synthetic intermediate for phosphorus fine chemicals (33), and it is still essential for those derived today from phosphorus trichloride. With the present work, we illustrate an alternative pathway to phosphorus chemicals originating with wet-process phosphate. It is clear that several classes of phosphorus chemicals will be accessible using the chemistry described here, passing through the key molecular intermediate bis(trichlorosilyl)phosphide

anion, a simple inorganic anion produced in a reaction using trichlorosilane, a high-production-volume chemical. In a possible future in which white phosphorus production were to cease, this methodology could be adopted as a replacement, keeping supply chains open for critical chemicals that currently rely on the manufacture of P₄.

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SUPPLEMENTARY MATERIALS

www.sciencemag.org/content/359/6382/1383/suppl/DC1
Materials and Methods
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Phosphoric acid as a precursor to chemicals traditionally synthesized from white phosphorus

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Silicon clears a wet path to phosphines

Phosphoric acid is produced on a massive scale for fertilizer by treating phosphate rock with sulfuric acid. In contrast, preparation of more elaborate phosphorus compounds used in chemical catalysis, pharmaceutical, and battery applications requires laborious generation and chlorination of elemental phosphorus. Geeson and Cummins now show that phosphoric acid may also be a practical source of such compounds (see the Perspective by Protasiewicz). They isolated and characterized a phosphide salt derived from treatment of dehydrated phosphoric acid with trichlorosilane, a compound already used at the commercial scale to produce high-purity silicon. The salt proved to be a versatile precursor for a range of alkylated and fluorinated phosphorus compounds.

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