Unprecedented Selective Aminolysis: Aminopropyl Phosphine as a Building Block for a New Family of Air Stable Mono-, Bis-, and Tris-Primary Phosphines

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Primary and secondary phosphines (RPH_2 and R_2PH) constitute an important class of organophosphorus compounds.[1−3] Their facile participation in a number of chemical reactions that include nucleophilic addition reactions with unsaturated species, substitution reactions with acid halides, reactions with alkali metals, and a host of reactions at the P^{III} center have resulted in the development of a large number of new chemical products of commercial significance.[1−8] Primary phosphines, in particular, have proven to be versatile starting materials for the development of hydroxyalkyl phosphines ($R_x(CH_2OH)_yP$) via formylation of P−H bonds with aldehydes.[9,10] The ease of transformation of P−H bonds into P−C bonds is, undoubtedly, a synthetic novelty and the hydroxymethylated-phosphorus compounds have provided a diverse range of chemical, catalytic, environmental, biological, and biomedical applications.[11−18]

A serious impediment to using primary and secondary phosphines as general-purpose reagents to develop new chemistry is associated with their unpleasant pyrophoric nature and extreme hydrolytic, thermal, and oxidative instabilities. In particular, primary phosphines with "user friendly" properties (e.g. good oxidative/thermal stability, low volatility) would be extremely important not only from the synthetic point of view but also for potential application (e.g. in dendrimers formation). As part of our ongoing research on the fundamental main group and organic chemistry of functionalized phosphorus compounds[19] we report, herein, unprecedented selectivity in the reaction of 3-aminopropyl primary phosphine **3**, with the methyl ester in the presence of free acid, amide, and thiol to produce air stable amide, carboxylate, and thiol functionalized primary phosphines (compounds **8**, **10**, **12**, and **14**, Scheme 1). The utility of conveniently accessible 3-aminopropylphosphine, $H_2N(CH_2)_3PH_2$ (**3**), as a building block for the development of a new air stable primary phosphine, as reported in this communication, is unique because highly dangerous phosphine gas (PH_3) and also alkalimetal metal phosphides (e.g. MPH_2; M = Li or Na) are routinely used in the synthesis of primary phosphine compounds.[1−3]

The synthon, 3-aminopropylphosphine **3**, was synthesized via an Arbuzov reaction of 1,3-dibromopropane with triethyl phosphite followed by conversion of the (3-bromopropyl)phosphonic acid diethyl ester **1** to the corresponding azide **2** (Scheme 1). The key synthon, (3-azidopropyl)phosphonic acid diethyl ester **2**, was produced in near quantitative yield as an analytically pure liquid by refluxing the bromophosphonate **1** and sodium azide in acetone.[20] It is important to recognize that the azide **2** is safe to handle as a neat liquid as well as in various organic solvents[21] (e.g.: THF, ether, acetone, and alcohol). In fact, the phosphonate functionalized alkyl azide **2** was produced in 100−200 g quantities. Routine safe handling procedures of hazardous chemicals is recommended. Further, the azide **2** upon reduction with LAH gave 3-aminopropylphosphine **3** in 65% yield.[22] 3-Aminopropylphosphine **3** is non-pyrophoric and is moderately stable in air. It can be stored for extended periods in a nitrogen atmosphere as a neat colorless liquid. It may be noted that the amine

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(20) **Preparation of (3-azidopropyl)phosphonic acid diethyl ester (2)**: A well-stirred solution of (3-bromopropyl)phosphonic acid diethyl ester (30 g, 115 mmol) and sodium azide (15 g, 230 mmol) in acetone (100 mL) was refluxed for 12 h in a nitrogen atmosphere, cooled to room temperature, and filtered, and solvent was removed under vacuum to afford diethyl-3-azidopropyl phosphonate, **2**, as a colorless liquid (25.5 g, 99%). ^1H ($CDCl_3$, 300 MHz): δ 4.2−4.0 (m, 4H), 3.4 (2H, t, J = 6.2 Hz), 1.95−1.7 (m, 4H), 1.3 (6H, t, J = 6.9 Hz). ^{13}C ($CDCl_3$, 75 MHz): δ 61.3, 50.9 (d, J = 16 Hz), 22.30 (d, J = 143 Hz), 21.9, 16.0. ^{31}P ($CDCl_3$, 121 MHz): δ 32.2. Mass (m/z): 222.2 $(M + H)^+$. HRMS, calcd for $C_7H_{16}O_3N_3P$ $(M + H)^+$ 222.1007, found 222.1005. Anal. Calcd for $C_7H_{16}N_3O_3P$: C, 38.01; H, 7.29; N, 18.99. Found: C, 38.04; H, 7.33, N, 19.01.
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(22) **Preparation of 3-aminopropylphosphine (3)**: To a vigorously stirred cold (0 °C) solution of LAH (230 mL, 1 M solution in ether) was added the solution of (3-azidopropyl)phosphonic acid diethyl ester **2** (30 g, 135 mmol) in ether (60 mL) during 1 h in a nitrogen atmosphere at room temperature for 4 h; the mixture was cooled to 0 °C and the excess of LAH was quenched by slow addition of cold aqueous brine solution (10 mL), followed by the addition of aqueous KOH solution (10%, 20 mL). The organic layer was separated, the aqueous layer was extracted with ether (3 × 300 mL), and the combined organic extract was washed with brine (100 mL), dried over anhydrous Na_2SO_4, and subjected to fractional distillation of the solvent under atmospheric pressure to afford 3-aminopropylphosphine, **3**, as a colorless liquid (8.0 g, 65%). 3-Aminopropyl phosphine **3** was isolated, stored, and used as 65% solution in ethanol. Satisfactory spectral and analytical data were obtained for **3** (see Supporting Information).

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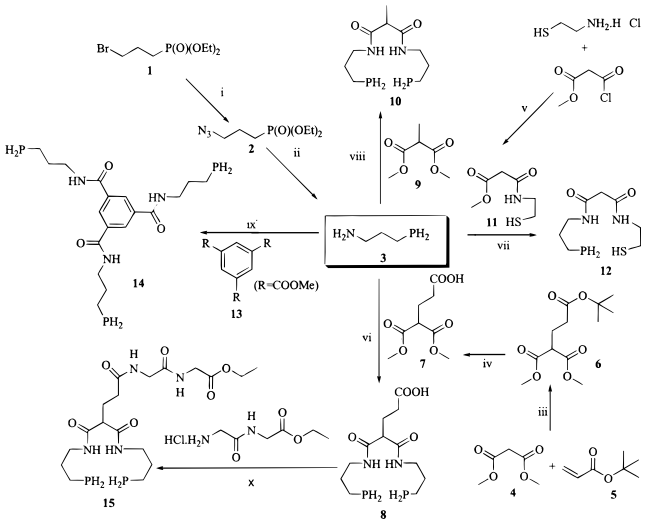
Scheme 1[a]



[a] Conditions: (i) NaN_3/acetone, reflux, 12 h, 99%. (ii) LAH, 4 h, 65%. (iii) K_2CO_3/benzene, $(Bu)_4N(HSO_4)$, reflux 12 h, 85%. (iv) TFA, room temperature, 12 h, 97%. (v) Et_3N, pyridine/CH_2Cl_2, 70%. (vi) 70 °C, 40 h, 51%. (vii) 100 °C, 12 h, 70%. (viii) 100 °C, 12 h, 70%. (ix) 100 °C, 12 h, 72%. (x) HBTU, CH_3CN, 65%.

functionalized primary phosphine **3** belongs to the family of aminoalkylphosphines and other functionalized alkyl primary phosphines reported by Stiles et al.[23] and Issleib et al.[24]

The synthetic utility of 3-aminopropylphosphine **3** for the development of a novel −COOH functionalized bisamidobisprimary phosphine, 4,4-bis(3-phosphanylpropylcarbamoyl)butyric acid (**8**), is depicted in Scheme 1. Thus, the precursor diester acid, 2-methoxycarbonylpentanedioic acid 1-methyl ester (**7**), was synthesized as shown in Scheme 1. It is remarkable to note that the "no solvent mediated" reaction of $NH_2(CH_2)_3PH_2$ (**3**) with the diester acid **7** is highly selective in that the −COOH group remained unattacked whereas the reaction occurred smoothly and selectively at the −COOMe groups to produce the novel carboxylate functionalized diamide bisprimary phosphine **8** in 51% yield.[25] The proton-coupled phosphorus NMR spectrum confirmed the presence of $-PH_2$ units in **8**. The compound **8** was fully characterized by ^1H, ^{13}C, and ^{31}P NMR spectroscopy and high-resolution mass spectrometry. It is important to recognize that the aminolysis of **7** with 3-aminopropylphosphine (**3**), when carried out in the presence of solvents (benzene or toluene), resulted in complex side reactions and the primary phosphine **8** was formed as a byproduct.

The nonphosphine synthetic route for bisprimary phosphine **8** is novel and prompted further investigation to test the generality of the reactions of 3-aminopropylphosphine (**3**) with functionalized esters. In fact, as shown in Scheme 1, the reactions of **3** with the functionalized esters **9**, **11**, and **13** produced a new generation of air-stable thiol functionalized (mono) **12**, amide functionalized (bis) **10**, and dendritic (tris) primary phosphines **14**, respectively in good yields.[26] The new primary phosphines **10**, **12**, and **14** were fully characterized by ^1H, ^{13}C, and ^{31}P NMR and high-resolution mass spectrometry. It is important to note that the reactions outlined in Scheme 1 proceed to completion in the absence of solvents and that the amide or thiol groups did not interfere in the aminolysis of the corresponding esters.

Combination of carboxylate and $-PH_2$ groups within the same molecule, as in compound **8** (N_2P_2COOH), will present unique prospects for attachment of phosphines to chemical and biochemical anchors via the traditional −COOH activation protocols.[27,28] To demonstrate the feasibility of linking −COOH groups of **8** with peptides (and proteins), a synthetic protocol for linking **8** with a dipeptide, gly gly ethyl ester hydrochloride, has been developed as outlined in Scheme 1. Thus, activation of the carboxylate of **8,** using HBTU, followed by reaction with the $-NH_2$ group of gly gly peptide produced P_2N_2gly gly peptide conjugate, {2-[4,4-bis(3-phosphanylpropylcarbamoyl)butyryalamino]acetylamino}acetic acid ethyl ester (**15**), in 65% yield. The oxidative stability of primary phosphine **8** is noteworthy because $-PH_2$ groups of **8** remained oxidatively inert during the reaction conditions that were employed for conjugation as well as silicagel column chromatographic purification procedures. The chemistry described in Scheme 1 demonstrates the utility of bifunctional phosphine frameworks, of type **8**, in combinatorial chemistry for the development of chelating unit functionalized peptide libraries.

The high thermal and oxidative instability of primary phosphines has often been a severe limitation to perform backbone chemical modifications while keeping the $-PH_2$ unit intact. In this context, the reactions at the $-NH_2$ functionality of the 3-aminopropylphosphine **3** (as summarized in Scheme 1) have provided a new approach toward the construction of amide, carboxylate, and thiol functionalized mono- or multinuclear primary phosphine compounds while maintaining the oxidative integrity of $-PH_2$ units. The non-phosphine (PH_3) synthetic route to the $H_2N(CH_2)_3PH_2$ (**3**), as demonstrated herein, is an important step toward exploring new chemistry of functionalized primary phosphines.

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Supporting Information Available: Experimental procedure and full characterization data for compounds **3**, **6**, **7**, **10**, **11**, **12**, **14**, and **15** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(26) **General procedure to prepare 10, 12, and 14:** The esters **9**, **11**, or **13** were heated at 100 °C with 3-aminopropylphosphine **3** (2.2 equiv for **9**, 1.2 equiv for **11**, and 3.3 equiv for **13**, respectively) for 12 h. Excess of 3-aminopropylphosphine **3** and methanol were removed under vacuum at 100 °C. The crude products **10**, **12**, or **14** were purified on a silica gel column under nitrogen to yield the pure **10**, **12,** or **14**. Satisfactory spectral and analytical data were obtained for the compounds **10**, **12**, or **14** (see Supporting Information).

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