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Single-stage synthesis of alkyl-*H*-phosphinic acids from elemental phosphorus and alkyl bromides

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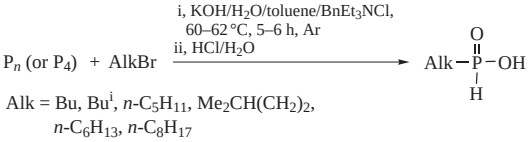
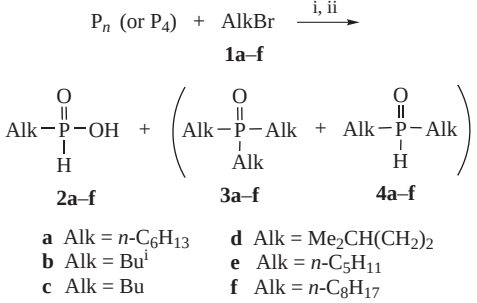
Elemental phosphorus (red or white) reacts with alkyl bromides at 60–62 °C in the phase-transfer catalytic system KOH/H_2O/PhMe/Et_3BnNCl to afford alkyl-*H*-phosphinic acids in up to 47% yield.



Organic *H*-phosphinic acids, RPH(O)(OH), are now widely explored and applied as prospective ligands for metal complex catalysts inducing many types of transformations,[1] drug precursors,[2] reagents for hydrometallurgy,[3] retardants,[4] surfactants[5] and building blocks for the preparation of in-demand phosphinic,[6] phosphonic[7] acids or other valuable compounds.[8] Therefore, search for the methods of convenient synthesis of organic *H*-phospinic acids is topical.[9] The traditional syntheses of these compounds are based on hydrolysis of harmful, aggressive and expensive alkyl- or aryldichlorophosphines.[10] In recent years, the methods for synthesis of phosphinic acids by the reactions of hypophosphorous acid, H_3PO_2 (prepared from white phosphorus[10]), with alkenes,[3,11] alkynes,[11(b)] and alkyl halides[11(a),(c)] were intensively developing. Usually, these reactions proceed in the presence of Pd catalysts,[11(a)–(c),12] under microwave activation[6(d)] or radical conditions.[3,13]

Here, we report on a facile one-pot synthesis of alkyl-*H*-phosphinic acids by the direct phosphorylation of alkyl bromides with elemental phosphorus in the presence of strong bases. Previously, we have shown[14] that alkyl bromides react with red phosphorus (P_n) in the KOH/H_2O/THF (or dioxane) system (the RBr:P_n:KOH ratio was 1:1.25:5) at 60–65 °C in the presence of triethylbenzylammonium chloride as the phase-transfer catalyst. The main products turned to be tertiary trialkylphosphine oxides $Alk_3P(O)$ (41–69% yields) while the yields of the corresponding practically useful[15] secondary dialkylphosphine oxides $Alk_2P(O)H$ did not exceed 4%. The formation of alkyl-*H*-phosphinic acids under these conditions did not occur.

After several experiments with red (P_n) or white (P_4) phosphorus and *n*-hexyl bromide **1a** (Scheme 1, Table 1, entries 1–6), synthetically reasonable conditions for the preparation of *n*-hexyl-*H*-phosphinic acid **2a** in 41–47% yield with good conversion



Scheme 1 *Reagents and conditions*: i, KOH/H_2O/PhMe/$BnEt_3NCl$, 50–80 °C, 5–6 h, argon; ii, HCl, H_2O, 20–25 °C.

Table 1 Synthesis of alkyl-*H*-phosphinic acids **2a–f** from elemental phosphorus and alkyl bromides **1a–f**.[a]

Entry	Alkyl bromide	Phosphorus	T/°C	Conversion of **1** (%)	Product	Yield of **2** (%)[b]
1	**1a**	P_n	50–52	78	**2a**	18 (23)
2	**1a**	P_4	50–52	78	**2a**	12 (15)
3	**1a**	P_n	60–62	92	**2a**	38 (41)
4	**1a**	P_4	60–62	70	**2a**	16 (23)
5[c]	**1a**	P_4	60–62	78	**2a**	37 (47)
6	**1a**	P_n	80	89	**2a**	23 (26)
7	**1b**	P_n	60–62	99	**2b**	7 (7)
8	**1c**	P_n	60–62	64	**2c**	12 (18)
9	**1c**	P_4	60–62	74	**2c**	19 (25)
10	**1d**	P_n	60–62	98	**2d**	11 (11)
11	**1e**	P_n	60–62	67	**2e**	25 (37)
12	**1e**	P_4	60–62	73	**2e**	32 (44)
13	**1f**	P_n	60–62	51	**2f**	15 (30)
14	**1f**	P_4	60–62	69	**2f**	19 (27)

[a] Molar ratio **1**:P:KOH:H_2O was 1:3.3:10:29, PhMe (1.67 ml mmol^{-1}), $BnEt_3NCl$ (17 mol%). [b] Isolated yields of **2** based on the loaded **1**. Yields based on the reacted **1** are given in parentheses. [c] Molar ratio **1**:P:KOH:H_2O was 1:3.3:14:31.

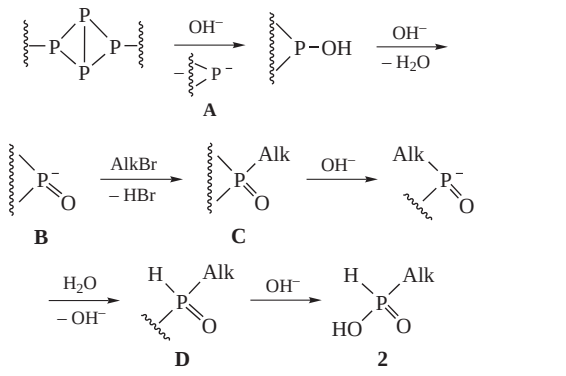
† *General procedure for synthesis of alkyl*-H-*phosphinic acids* **2a–f** *from red phosphorus and alkyl bromides.* A solution of KOH·0.5H_2O (20 g, 307 mmol) in water (13 ml) was added dropwise at 40 °C (argon) for 10 min to a mixture of red phosphorus (3.10 g, 100 mg-atom), toluene (50 ml) and $BnEt_3NCl$ (0.4 g). The resulted reaction mixture was heated to 60–62 °C, and the solution of corresponding alkyl bromide **1** (30 mmol) in toluene (10 ml) was added dropwise for 40 min. Then the mixture was stirred at 60–62 °C for 5 h, cooled to room temperature and diluted with water (80 ml). The aqueous and toluene layers were separated. The aqueous layer was extracted with chloroform (3×30 ml) to give extract A. The remaining aqueous layer was acidified with 15% aqueous HCl to pH 4–5, extracted with chloroform (3×30 ml) to deliver extract B, which was dried with $CaCl_2$, evaporated, and the residue was dried at 40 °C (1 Torr) to give alkylphosphinic acids **2a–f**.

of bromide **1a** (78–92%) were disclosed.† The essential change in the equivalent ratio **1a** : P : KOH (from 1 : 1.25 : 5 up to 1 : 3.33 : 8–9) and conducting the process in toluene instead of THF was the crucial prerequisite, the optimal reaction temperature having been 60–62 °C. Acid **2a** was isolated from the reaction mixture by extraction of the aqueous layer after its acidification. The residue after concentrating the toluene organic layer contained trihexyl- and dihexylphosphine oxides **3a**, **4a** in the ratio of ~1 : 2 and in the total yield of ~36% (the ^{31}P NMR data). Note that for driving the reaction towards acid **2a** it was necessary to slowly add (dropwise) a toluene solution of *n*-hexyl bromide **1a** to the P/KOH/H_2O/PhMe/$BnEt_3NCl$ system.†

Diverse alkyl bromides **1b**–**f** were then examined in the reaction with elemental phosphorus (see Table 1). *n*-Alkyl-*H*-phosphinic acids **2c**,**e**,**f** were obtained in moderate or good yields. The exceptions were acids **2b** and **2d** obtained in 7 and 11% yields, respectively (entries 7 and 10), which can be explained by side hydrolysis and/or dehydrobromination of the starting isoalkyl bromides **1b**,**d** under the action of potassium hydroxide.

The hydrophosphorylation of alkyl bromides herein studied proceeds likely *via* the initial formation of polyphosphide **A** and polyphosphinite **B** anions resulted from the disassembling of P_n or P_4 lattice under the action of hydroxide anion.[16] The nucleophilic reaction of polyphosphinite anions **B** with alkyl bromide and the consecutive cleavage of the remaining P–P bonds in the intermediates **C** and **D** by hydroxide anions lead finally to phosphinic acids **2** (Scheme 2).

In summary, a single-stage convenient synthesis of alkyl-*H*-phosphinic acids from alkyl bromides and elemental phosphorus (red or white) under phase transfer conditions (aqueous solution of KOH/PhMe/$BnEt_3NCl$) has been developed. The reaction easily proceeds at 60–62 °C when the equivalent ratio AlkBr : P : KOH = = 1 : 3.33 : (10–14) is applied.



Scheme 2

Chloroform extract A and toluene layer were combined, the volatiles were removed *in vacuo*, the residue (data are given for reaction with hexyl bromide **1a**, 0.4 g was returned) contained 1.15 g of a mixture of *n*-$Hex_2P(O)H$ (δ_P 32 ppm) and *n*-$Hex_3P{=}O$ (δ_P 45 ppm) in the ratio of 2 : 1 (see the ^{31}P NMR data, Online Supplementary Materials). The conversions of alkyl bromides **1a**–**f** were 92, 99, 64, 98, 67 and 51%, respectively (the conversions of **1b**–**e** were determined by ^{1}H NMR using CH_2Cl_2 as internal standard; in the cases of **1a** and **1f**, they were distilled from the chloroform–toluene solutions).

n-*Hexyl*-H-*phosphinic acid* **2a**. Isolated yield 1.85 g (38%, P_n) or 2.12 g (37%, P_4); light yellow oil. ^{1}H NMR ($CDCl_3$) δ: 0.85 (t, 3H, Me, ^3J 6.8 Hz), 1.29–1.38 [m, 6H, $(CH_2)_3$], 1.57 (m, 2H, CH_2Bu), 1.72 (m, 2H, CH_2P), 7.00 (d, 1 H, PH, $^1J_{HP}$ 545 Hz), 11.7 (s, 1H, OH). ^{31}P NMR ($CDCl_3$) δ: 38.8 (d, $^1J_{PH}$ 545 Hz); lit.,[8(e)] δ_P 39.07 ($^1J_{PH}$ 540 Hz). Found (%): C, 48.29; H, 9.8; P, 20.82. Calc. for $C_6H_{15}O_2P$ (%): C, 47.99; H, 10.07; P, 20.63.

For characteristics of compounds **2b**–**f**, see Online Supplementary Materials.

Under analogous conditions, phosphinic acids **2a**,**c**,**e**,**f** were prepared in the yields of 19–32% from white phosphorus (50 mg-atom), alkyl bromides **1a**,**c**,**e**,**f** (30 mmol), KOH·0.5H_2O (13.00 g, 200 mmol), $BnEt_3NCl$ (0.2 g), toluene (30 ml) and water (6.5 ml) (see Table 1).

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2019.05.030.

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