

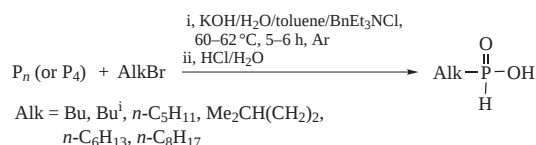
Single-stage synthesis of alkyl-*H*-phosphinic acids from elemental phosphorus and alkyl bromides

Nina K. Gusarova, Anastasiya O. Sutyryna, Vladimir A. Kuimov, Svetlana F. Malysheva,
Natalia A. Belogorlova, Pavel A. Volkov and Boris A. Trofimov*

A. E. Favorsky Irkutsk Institute of Chemistry, Siberian Branch of the Russian Academy of Sciences,
664033 Irkutsk, Russian Federation. Fax: +7 3952 419 346; e-mail: boris_trofimov@iroch.irk.ru

DOI: 10.1016/j.mencom.2019.05.030

Elemental phosphorus (red or white) reacts with alkyl bromides at 60–62 °C in the phase-transfer catalytic system KOH/H₂O/PhMe/Et₃BnCl to afford alkyl-*H*-phosphinic acids in up to 47% yield.

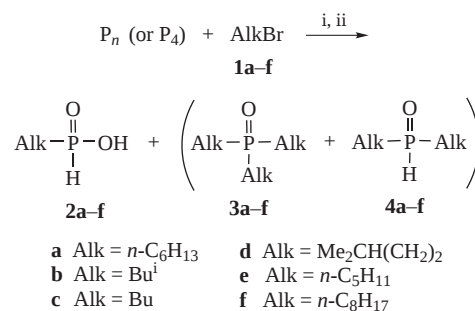


Organic *H*-phosphinic acids, RPH(O)(OH), are now widely explored and applied as prospective ligands for metal complex catalysts inducing many types of transformations,¹ drug precursors,² reagents for hydrometallurgy,³ retardants,⁴ surfactants⁵ and building blocks for the preparation of in-demand phosphinic,⁶ phosphonic⁷ acids or other valuable compounds.⁸ Therefore, search for the methods of convenient synthesis of organic *H*-phosphinic acids is topical.⁹ The traditional syntheses of these compounds are based on hydrolysis of harmful, aggressive and expensive alkyl- or arylchlorophosphines.¹⁰ In recent years, the methods for synthesis of phosphinic acids by the reactions of hypophosphorous acid, H₃PO₂ (prepared from white phosphorus¹⁰), 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 shown¹⁴ that alkyl bromides react with red phosphorus (P_n) in the KOH/H₂O/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 Alk₃P(O) (41–69% yields) while the yields of the corresponding practically useful¹⁵ secondary dialkylphosphine oxides Alk₂P(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 (P₄) 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/H₂O/PhMe/BnEt₃NCl, 50–80 °C, 5–6 h, argon; ii, HCl, H₂O, 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:H₂O was 1:3.3:10:29, PhMe (1.67 ml mmol^{–1}), BnEt₃NCl (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:H₂O 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·0.5H₂O (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 BnEt₃NCl (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 CaCl₂, 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 ³¹P 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/H₂O/PhMe/BnEt₃NCl 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 P₄ 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/BnEt₃NCl) 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.

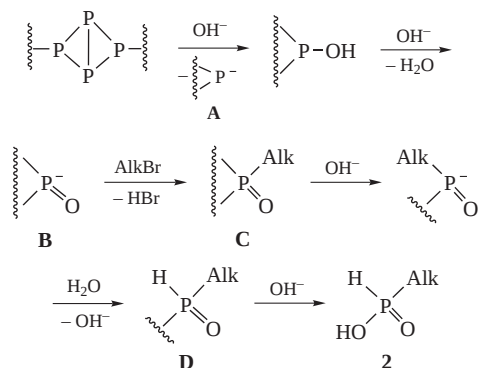
This work was supported by the Russian Science Foundation (grant no. 18-73-10080). The main results were obtained using the equipment of Baikal Analytical Center of Collective Using, Siberian Branch of the Russian Academy of Sciences.

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.

References

- (a) R. Pothiraja, S. Shanmugan, M. G. Walawalkar, M. Nethaji, R. J. Butcher and R. Murugavel, *Eur. J. Inorg. Chem.*, 2008, 1834; (b) S. Luo, K. M. Macauley and J. T. Poulton, *Patent EP 2075266*, 2009; (c) D. Yakhvarov, E. Trofimova, O. Sinyashin, O. Kataeva, Y. Budnikova, P. Lönnecke, E. Hey-Hawkins, A. Petr, Y. Krupskaya, V. Kataev, R. Klingeler and B. Büchner, *Inorg. Chem.*, 2011, **50**, 4553; (d) E. A. Trofimova, A. B. Dobrynin, T. P. Gerasimova, S. A. Katsyuba, O. G. Sinyashin and D. G. Yakhvarov, *Mendeleev Commun.*, 2013, **23**, 135; (e) E. A. Trofimova, A. B. Dobrynin, O. G. Sinyashin and D. G. Yakhvarov, *Butlerovskie Soobshcheniya*, 2013, **33**, 49 (in Russian); (f) D. G. Yakhvarov, E. A. Trofimova, A. B. Dobrynin, T. P. Gerasimova, S. A. Katsyuba and O. G. Sinyashin, *Mendeleev Commun.*, 2015, **25**, 27.
- (a) W. Froestl, S. J. Mickel, R. G. Hall, G. Vonsprecher, D. Strub, P. A. Baumann, F. Brugger, C. Gentsch, J. Jaekel, H. R. Olpe, G. Rihs, A. Vassout, P. C. Waldmeier and H. Bittiger, *J. Med. Chem.*, 1995, **38**, 3297; (b) W. Froestl, S. J. Mickel, G. Vonsprecher, P. J. Diel, R. G. Hall, L. Maier, D. Strub, V. Melillo, P. A. Baumann, R. Bernasconi, C. Gentsch, K. Hauser, J. Jaekel, G. Karlsson, K. Klebs, L. Maitre, C. Marescaux, M. F. Pozza, M. Schmutz, M. W. Steinmann, H. Vanriezen, A. Vassout, C. Mondadori, H. R. Olpe, P. C. Waldmeier and H. Bittiger, *J. Med. Chem.*, 1995, **38**, 3313; (c) A. V. Vinyukov, A. V. Borodachev, A. S. Starikov, A. V. Afanasyev, M. E. Dmitriev, B. V. Lednev and V. V. Ragulin, *Mendeleev Commun.*, 2018, **28**, 295.
- I. E. Nifant'ev, M. E. Minyaev, A. N. Tavtorkin, A. A. Vinogradov and P. V. Ivchenko, *RSC Adv.*, 2017, **7**, 24122.
- R. Du, J. Xu, Q. Cheng, S. Yuan, L. Wang and T. Guo, *Patent WO 2014101346 A1*, 2014.
- (a) E. S. Ermolaev, *PhD Thesis*, Kazan, 2008; (b) F. D. Wang, R. Tang and W. E. Buhro, *Nano Lett.*, 2008, **8**, 3521.
- (a) F. H. Ebetino, D. L. Soper, M. J. Dirr, M. W. Lundy, G. Mielsing, J. A. Wos, M. A. deLong and X. Liu, *Phosphorus Sulfur Silicon Relat. Elem.*, 2002, **177**, 1725; (b) A. S. Kende, H.-Q. Dong, X. Liu and F. H. Ebetino, *Tetrahedron Lett.*, 2002, **43**, 4973; (c) K. V. Alferov, N. G. Faleev, E. N. Khurs, Yu. N. Zhukov and R. M. Khomutov, *Mendeleev Commun.*, 2002, **12**, 2; (d) M. Kalek and J. Stawinski, *Tetrahedron*, 2009, **65**, 10406; (e) M. S. Markoulides and A. C. Regan, *Org. Biomol. Chem.*, 2013, **11**, 119; (f) N. Z. Kiss, Z. Rádai, I. Tihanyi, T. Szabó and G. Keglevich, *Mendeleev Commun.*, 2018, **28**, 31.
- (a) G. E. Liñares, E. L. Ravaschino and J. B. Rodriguez, *Curr. Med. Chem.*, 2006, **13**, 335; (b) C. M. Sevrain, M. Berchel, H. Couthon and P.-A. Jaffrès, *Beilstein J. Org. Chem.*, 2017, **13**, 2186.
- (a) X. Liu, X. E. Hu, X. Tian, A. Mazur and F. H. Ebetino, *J. Organomet. Chem.*, 2002, **646**, 212; (b) A. Gautier, G. Garipova, C. Salcedo, S. Balieu and S. R. Piettre, *Angew. Chem., Int. Ed.*, 2004, **43**, 5963; (c) L. Coudray, K. Bravo-Altamirano and J.-L. Montchamp, *Org. Lett.*, 2008, **10**, 1123; (d) M. Ordóñez, H. Rojas-Cabrera and C. Cativiela, *Tetrahedron*, 2009, **65**, 17; (e) P. Troupa, G. Katsioulari and S. Vassiliou, *Synlett*, 2015, **26**, 2714; (f) Y. He, H. Wu and F. D. Toste, *Chem. Sci.*, 2015, **6**, 1194.
- A. V. Artem'ev, A. O. Sutyryna, E. A. Matveeva, A. I. Albanov and L. V. Klyba, *Mendeleev Commun.*, 2017, **27**, 137.
- (a) N. N. Greenwood and A. Earnshaw, *Chemistry of the Elements*, 2nd edn., Butterworth-Heinemann, Oxford, 1997; (b) D. E. C. Corbridge, *Phosphorus: Chemistry, Biochemistry and Technology*, 6th edn., CRC Press, Boca Raton, 2013.
- (a) J.-L. Montchamp, *J. Organomet. Chem.*, 2005, **690**, 2388; (b) L. Coudray and J.-L. Montchamp, *Eur. J. Org. Chem.*, 2008, 3601; (c) J.-L. Montchamp, *Acc. Chem. Res.*, 2014, **47**, 77; (d) D. Virieux, J.-N. Volle, N. Bakalara and J.-L. Pirat, in *Phosphorus Chemistry*, ed. J.-L. Montchamp, Springer, London, 2015, vol. 1, pp. 39–115.



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*-Hex₂P(O)H (δ_P 32 ppm) and *n*-Hex₃P=O (δ_P 45 ppm) in the ratio of 2:1 (see the ³¹P 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 ¹H NMR using CH₂Cl₂ 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%, P₄); light yellow oil. ¹H NMR (CDCl₃) δ : 0.85 (t, 3H, Me, ³J 6.8 Hz), 1.29–1.38 [m, 6H, (CH₂)₃], 1.57 (m, 2H, CH₂Bu), 1.72 (m, 2H, CH₂P), 7.00 (d, 1H, PH, ¹J_{HP} 545 Hz), 11.7 (s, 1H, OH). ³¹P NMR (CDCl₃) 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 C₆H₁₅O₂P (%): 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·0.5H₂O (13.00 g, 200 mmol), BnEt₃NCl (0.2 g), toluene (30 ml) and water (6.5 ml) (see Table 1).

- 12 (a) S. Deprele and J.-L. Montchamp, *J. Am. Chem. Soc.*, 2002, **124**, 9386; (b) K. Bravo-Altamirano and J.-L. Montchamp, *Org. Lett.*, 2006, **8**, 4169.
- 13 (a) S. Deprele and J.-L. Montchamp, *J. Org. Chem.*, 2001, **66**, 6745; (b) K. D. Troev, *Reactivity of P–H Group of Phosphorus Based Compounds*, Academic Press, London, 2018.
- 14 (a) N. K. Gusarova, S. F. Malysheva, T. N. Rakhmatulina, V. I. Dmitriev, S. I. Shaikhutdinova, L. M. Sinegovskaya and B. A. Trofimov, *Zh. Obshch. Khim.*, 1990, **60**, 828 (in Russian); (b) S. F. Malysheva, Z. M. Garashchenko, S. N. Arbuzova, M. V. Nikitin, N. K. Gusarova and B. A. Trofimov, *Russ. J. Gen. Chem.*, 1997, **67**, 1794 (*Zh. Obshch. Khim.*, 1997, **67**, 1905).
- 15 (a) V. I. Men'shikov, I. Yu. Voronova, O. A. Proidakova, S. F. Malysheva, N. I. Ivanova, N. A. Belogorlova, N. K. Gusarova and B. A. Trofimov, *Russ. J. Appl. Chem.*, 2009, **82**, 183 (*Zh. Prikl. Khim.*, 2009, **82**, 189); (b) K. C. Pitchaiah, K. Sujatha, C. V. S. Brahmananda Rao, S. Subramaniam, N. Sivaraman and P. R. Vasudeva Rao, *Radiochim. Acta*, 2015, **103**, 245; (c) A. Leoncini, J. Huskens and W. Verboom, *Chem. Soc. Rev.*, 2017, **46**, 7229.
- 16 B. A. Trofimov and N. K. Gusarova, *Mendeleev Commun.*, 2009, **19**, 295.

Received: 31st October 2018; Com. 18/5730