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Synthesis of alkyl-*H*-phosphinic acid alkyl esters from red phosphorus and alkyl bromides

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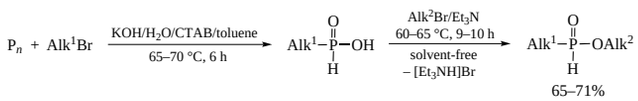
Alkyl-*H*-phosphinic acid alkyl esters are synthesized in 65–71% yield *via* chemoselective reaction of alkyl bromides with available alkyl-*H*-phosphinic acids (60–65 °C, Et_3N). The latter are prepared, in turn, by direct phosphorylation of alkyl bromides with red phosphorus under phase-transfer conditions.



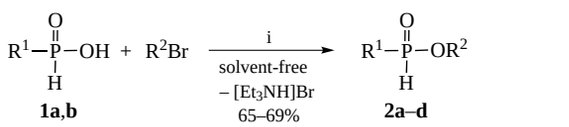
Keywords: alkyl esters, alkyl-*H*-phosphinic acids, red phosphorus, alkyl bromides, esterification, alkylation.

H-Phosphinate esters of the aromatic type, ArPH(O)(OAr′), ArPH(O)(OAlk) or AlkPH(O)(OAr), are attractive targets for the design of prospective ligands for metal complex catalysts,[1] drug precursors,[2] particularly, fosinopril, fosdevirine, lesogaberan,[2(*a*)] flame retardant additives,[3] extractants,[4] as well as reactive reagents in organic and organoelement synthesis.[5] Less studied alkyl-*H*-phosphinic acid alkyl esters are also prospective building blocks, *e.g.*, in addition reactions to double and triple carbon–carbon bonds.[6] However, alkyl alkyl-*H*-phosphinates still remain a hard-to-reach class of organophosphorus substrates. The known method for their synthesis includes alkylation of P–H bond in alkyl phosphinates $AlkOP(O)H_2$ with alkyl halides in the presence of strong bases such as Pr^{i}ONa, MeONa, DBU, BuLi, which requires specific conditions.[6(*a*),7]

As for the esterification of the hydroxy group of phosphinic acids, AlkPH(O)OH, it is limited to one work, where the esterification of octyl-*H*-phospinic acid with toxic organosilicate $Si(OMe)_4$ by refluxing in toluene was attempted.[8] However, the target methyl octyl-*H*-phosphinate has not been isolated and characterized. To the best of our knowledge, there are no literature data on simple alkylation of alkyl-*H*-phosphinic acids with alkyl halides.

Herein, we report the first example of chemoselective and effective synthesis of alkyl alkyl-*H*-phosphinates by the alkylation of alkyl-*H*-phosphinic acids with alkyl bromides. Alkyl-*H*-phosphinic acids became available *via* chemoselective direct one-pot alkylation/oxidation of elemental (white and red) phosphorus in the multi-phase alkyl bromide/KOH/H_2O/toluene system with the use of alkyl-PEG recyclable micellar catalysts.[9] We started our experiments with the search for optimal conditions for the alkylation of *n*-alkyl-*H*-phosphinic acids. As a reference for this investigation, the reaction between model *n*-octyl-*H*-phosphinic acid **1a** and *n*-butyl bromide was chosen (Scheme 1, Table 1).

As can be seen from the presented data, at an equimolar ratio of the reactants at room temperature in the absence of a solvent, the reaction does not occur (see Table 1, entry 1). A positive result was achieved by heating the reaction mixture to 80–85 °C for 5 h, however, in this case, the conversion of the starting *H*-phosphinic acid **1a** was incomplete, and the yield of butyl octyl-*H*-phosphinate **2a** did not exceed 50% (entry 2). Increasing the amount of butyl bromide to 2 equivalents (entry 3) only slightly improved the yield of the alkylation product (54%). The conditionally optimal amount of BuBr with a significant enhancement of the alkylation process efficiency turned out to be 3 molar equivalents relative to the acid **1a** (entry 4, 60–65 °C, 9 h, the yield of **2a** was 69%). The use of a five- or sevenfold excess of the starting BuBr led only to a slight reduction of the reaction time while the yield of **2a** remained practically the same



1a,**b**

a R^1 = *n*-C_8H_{17}
b R^1 = *n*-C_6H_{13}

2a–d

a R^1 = *n*-C_8H_{17}, R^2 = Bu
b R^1 = *n*-C_6H_{13}, R^2 = Et
c R^1 = *n*-C_6H_{13}, R^2 = Bu
d R^1 = *n*-C_8H_{17}, R^2 = *n*-C_6H_{13}

Scheme 1 *Reagents and conditions*: i, Et_3N, 60–65 °C, 9–10 h, solvent-free.

Table 1 Optimization of the alkylation conditions.

Entry	Conditions[a]	**1a**/BuBr molar ratio	*T*/°C	*t*/h	Yield of **2a** (%)
1	A	1 : 1	20–25	24	0
2	A	1 : 1	80–85	5	50
3	A	1 : 2	60–65	12	54
4	A	**1 : 3**	**60–65**	**9**	**69**
5	A	1 : 5	60–65	7	71
6	A	1 : 7	60–65	6	72
7	A	1 : 3	40–45	21	57
8	B	1 : 3	60–65	20	30
9	C	1 : 3	60–65	20	0

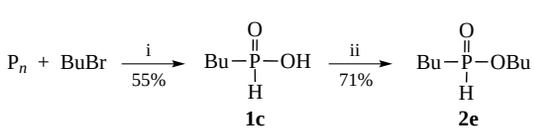
[a] Conditions: A, acid **1a** (3 mmol), Et_3N (3.3 mmol), solvent-free; B, MeCN (2 ml) added; C, pyridine (3.3 mmol) used as a base instead of Et_3N.

(entries 5 and 6). However, such a large molar excess of alkyl bromide is not appropriate from the process atom economy point of view. Carrying out the reaction under milder conditions at 40–45 °C (entry 7) led, along with a significant increase in the reaction time (21 h), to a decrease in the phosphinate **2a** yield (57%). The change of the base from triethylamine to pyridine decelerated the process drastically, and product **2a** was not formed at all (entry 9).

Noteworthy, according to ^{31}P NMR monitoring data, the content of the target phosphinate **2a** in the reaction mixture reached ~90%, however, its isolated yields did not exceed 69–72%. The possible explanation for this fact may be the partial hydrolysis of the target ester during its isolation by column chromatography on SiO_2. The possibility of alkyl-*H*-phosphinate hydrolysis was confirmed experimentally. In particular, heating butyl octyl-*H*-phosphinate **2a** in an ethanol solution at 70–75 °C in the presence of 3–4 equiv. of water for 4 h led to its complete hydrolysis to the corresponding octyl-*H*-phosphinic acid **1a** (^{31}P NMR data).

The optimal reaction conditions were successfully extended both to other *H*-phosphinic acids and to various alkyl bromides. The reaction of alkyl-*H*-phosphinic acids **1a**,**b** with butyl, ethyl and hexyl bromides proceeded at 60–65 °C for 9–10 h chemoselectively (only alkylation of the hydroxy group was observed) to form the corresponding alkyl alkyl-*H*-phosphinates **2a**–**d** in 65–69% yield (see Scheme 1).† Phosphinic acids **1a**,**b** with longer alkyl substituents were here employed as more accessible by a novel one-pot their synthesis basing on direct alkylation of red phosphorus.[9]

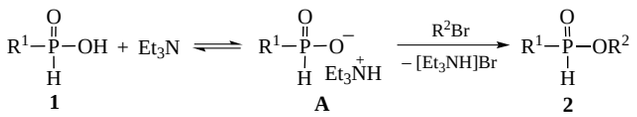
Further, we decided to improve the previously developed method for the synthesis of alkyl-*H*-phosphinic acids from red phosphorus P_n and alkyl bromides. In earlier work[9(*d*)] the yield of butyl-*H*-phosphinic acid **1c** in this reaction (85–90 °C, KOH/H_2O/toluene/alkyl-PEG catalyst) was limited to only 21%. After the series of experiments, we found that the use of cetyltrimethylammonium bromide (CTAB) as a phase-transfer catalyst and lowering the temperature to 65–70 °C allowed us to increase the yield of butylphosphinic acid **1c** to 55% (Scheme 2).‡



Scheme 2 *Reagents and conditions*: i, KOH, H_2O, CTAB, toluene, 65–70 °C, 6 h; ii, BuBr, Et_3N, 60–65 °C, 9 h, solvent-free.

† *Reaction of alkyl*-H-*phosphinic acids* **1a**,**b** *with alkyl bromides (general procedure).* A mixture of alkyl-*H*-phosphinic acid **1** (3 mmol), *n*-alkyl bromide (9 mmol) and triethylamine (3.3 mmol, 303 mg) was stirred under an argon atmosphere at 60–65 °C for 9–10 h. Then, Et_2O (4 ml) was added, the precipitated triethylammonium bromide was filtered off and additionally washed with Et_2O (2 × 3 ml). The combined filtrate was evaporated under reduced pressure. The residue was purified by column chromatography on SiO_2 (eluent: ethyl acetate/MeCN, 3 : 1) to give the target alkyl alkyl-*H*-phosphinate **2**.

‡ *Reaction of red phosphorus with butyl bromide (general procedure).* A mixture of red phosphorus (3.1 g, 100 mmol), CTAB (1.1 g, 0.05 mmol), solution of KOH · 0.5 H_2O (20.0 g, 307 mmol) in water (722 mmol, 13 ml), and toluene (50 ml) was heated under an argon atmosphere to 65–70 °C. Then, a solution of butyl bromide (4.11 g, 30 mmol) in toluene (10 ml) was added dropwise for 2 h, and the reaction mixture was additionally stirred at 65–70 °C for 4 h. The reaction mixture was cooled to room temperature, water (50 ml) was added, the aqueous layer was separated, acidified with HCl to pH 5 and extracted with dichloromethane (3 × 50 ml). The organic extract was dried over sodium sulfate, and the solvent was evaporated. The residue was dried under reduced pressure to give the target butyl-*H*-phosphinic acid **1c** (2.0 g, 55% yield).



Scheme 3

Acid **1c** thus obtained was used for the synthesis of butyl butyl-*H*-phosphinate **2e** under the conditions developed above (Scheme 2).

The formation of alkyl alkyl-*H*-phosphinates (Scheme 3) is probably initiated by deprotonation of alkyl-*H*-phosphinic acid **1** with triethylamine leading to the corresponding salt **A**. Then, alkylation of O-centered anion with alkyl bromide completes the formation of the target phosphinate **2**. As a by-product, triethylammonium bromide is also identified in the reaction mixture.

In conclusion, based on red phosphorus and commercially available alkyl bromides a convenient two-stage chemoselective method for the synthesis of in-demand class of organophosphorus substrates, *viz.* alkyl alkyl-*H*-phosphinates, promising drug precursors, ligands for the design of metal complexes, as well as building blocks in organic and organoelement synthesis, has been developed. The synthesized alkyl-*H*-phosphinic acid alkyl esters can be used, in particular, as initial reagents in the original S_N^HAr reactions with pyridinoids.[10]

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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.2022.11.028.

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