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# Phosphorus halide free synthesis of 1,2,3,4-tetrahydroisophosphinoline 2-oxides

**Svetlana F. Malysheva, Nina K. Gusarova, Natalia A. Belogorlova, Anastasiya O. Sutyrina, Alexander I. Albanov, Boris G. Sukhov, Vladimir A. Kuimov, Yuriy I. Litvintsev and Boris A. Trofimov***

*A. E. Favorsky Irkutsk Institute of Chemistry, Siberian Branch of the Russian Academy of Sciences, 664033 Irkutsk, Russian Federation. Fax: +7 395 241 9346; e-mail: boris_trofimov@irioch.irk.ru*

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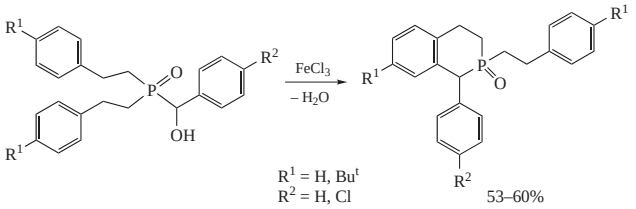
**The herein developed phosphorus halide free synthesis of 1,2,3,4-tetrahydroisophosphinoline 2-oxides involves intramolecular heterocyclization of *P*,*P*-bis(2-arylethyl)-*P*-(α-hydroxybenzyl)phosphine oxides, available from styrenes, phosphine and aldehydes. The cyclization proceeds in the presence of $FeCl_3$ at 80 °C, yield of the products is 53–60%.**

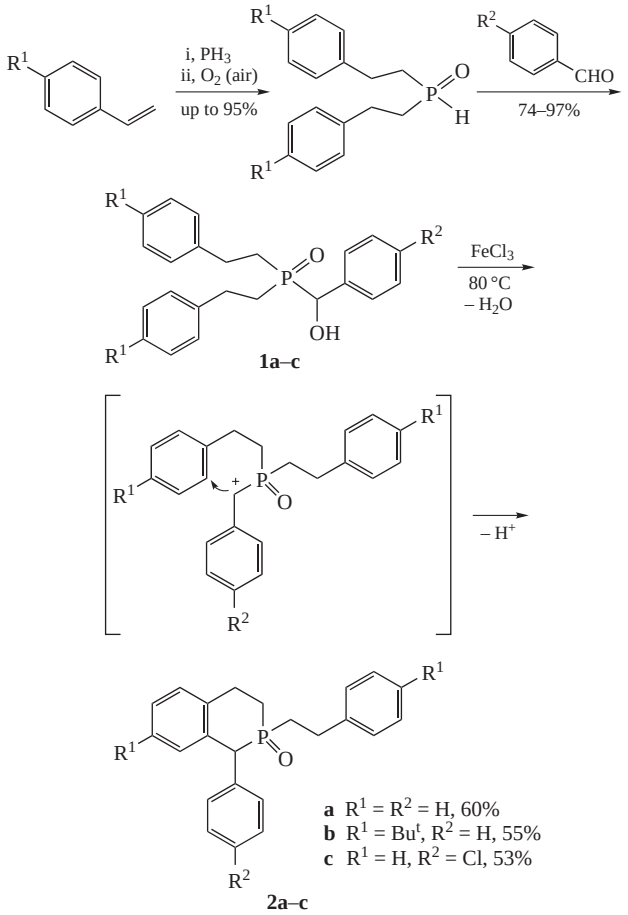



The phosphorus-containing heterocyclic compounds,[1] continue to attract significant attention from researchers. Among them, isophospinolines and their oxides are of interest as prospective ligands for metal complex catalysts.[1(a),(c)] Also, they can be used as complexing agents in the anti-corrosion compositions,[1(d)] antistatic components,[1(e)] additives to electrolytes[1(f)] and building blocks for design of electroluminescent materials[1(g),(h)] or solar panels.[1(i)]

At the same time, the known routs to isophosphinoline core[1(b),(c),2] are based on malignant and aggressive reagents. For instance, tetrahydroisophosphinoline 2-oxides have been recently prepared from β-hydroxy phosphine oxides whose synthesis is multistep and requires the use of phosphorus halides and BuLi.[2(a),(c),(d)] Therefore, the development of an expedient access to tetrahydroisophosphinoline oxides free of $PHal_3$ and organometallic reagents represents a clear-card challenge.

In this communication, we describe a facile synthesis of 1,2,3,4-tetrahydroisophosphinoline 2-oxides **2a**–**c** by intramolecular heterocyclization of *P*,*P*-bis(2-arylethyl)-*P*-(α-hydroxybenzyl)phosphine oxides **1a**–**c** (Scheme 1). The latter are now easily available from red phosphorus (*via* phosphine/hydrogen mixture), styrenes and aldehydes.[3–5] The heterocyclization has been accomplished by heating α-hydroxy phosphine oxides **1a**–**c** (80 °C, 10–20 h, chlorobenzene) in the presence of $FeCl_3$, the yield of benzophosphorinane oxides **2a**–**c** being 53–60%.†

The monitoring ($^{31}P$ NMR) of the reaction has shown that signal intensity of the initial phosphine oxides **1a**–**c** (49–50 ppm) decreases, whereas that of the target phosphorinane heterocycles **2a**–**c** (42–43 ppm) grows. In the $^1H$ NMR spectra of compounds **2a**–**c**, multiplets of phosphorinane cycle ($H_{ax}$-4, $H_{eq}$-4) resonate in the region 2.90, 3.20, and characteristic doublet of H-1 proton is located at 4.15 ppm. The signal of H-3 protons is always overlapped with that for the protons of $CH_2P$ group at 2.00 ppm. In the $^{13}C$ NMR spectra of **2a**–**c**, characteristic signals of phosphorinane cycle are $C^3$, $C^4$ and $C^1$ at 23, 27 and 48 ppm, respectively.




**Scheme 1**

† For details of synthesis of compounds **1a**–**c**, see Online Supplementary Materials.

*Synthesis of 1,2,3,4-tetrahydroisophosphinoline 2-oxides* **2a**–**c** *(general procedure)*. A mixture of α-hydroxy phosphine oxide **1a**–**c** (1.0 mmol), chlorobenzene (5 ml) and $FeCl_3$ (2.0 mmol) was stirred at 80 °C for 10 h (**1a**), 20 h (**1b**) or 15 h (**1c**). The reaction progress was monitored by TLC (chloroform as eluent). The mixture was then diluted with water (twice), extracted with chloroform (3 × 3 ml). The chloroform extract was washed with water (3 × 1 ml), dried over $K_2CO_3$, chloroform was removed, the residue was dissolved in diethyl ether (3 × 2 ml) and filtered. The filtrate was concentrated, the residue was dried *in vacuo* to give products **2a**–**c**.

As shown on the example of hydroxyphosphine oxide **1a**, the use of $ZnCl_2$ or phosphoric acid as catalysts was unreasonable: yield of benzophosphorinane oxide **2a** as well as selectivity of the heterocyclization noticeably decreased. When the reaction was implemented in $FeCl_3$/toluene, the yield of compound **2a** did not exceed 20%, whereas in the $AlCl_3$/toluene system or in the aqueous (50%) $H_2SO_4$ heterocyclization of hydroxy phosphine oxide **1a** did not occur. Upon refluxing ($FeCl_3$ as a catalyst) in benzonitrile, THF, dichloromethane or dichloroethane, the formation of product **2a** was not detected.

In conclusion, an expedient strategy for the $PCl_3$-free synthesis of a novel group of benzophosphorinanes, namely, benzophosphorinane oxides, from red phosphorus, styrenes and aldehydes has been developed. The major novelty of the methodology is heterocyclization of now available α-hydroxy-(2-arylethyl)phosphine oxides in the presence of acids. The target benzophosphorinane oxides are prospective ligands for metal complex catalysts and intermediates for design of luminescent and optic materials. The results obtained contribute to the chemistry of both elemental phosphorus and phosphorus-containing heterocycles.

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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.2018.01.008.

*1-Phenyl-2-(2-phenylethyl)-1,2,3,4-tetrahydroisophosphinoline 2-oxide* **2a**: isolated yield 208 mg (60%), colourless crystalline solid, mp 80–85 °C (hexane). $^1$H NMR (400.13 MHz, $CD_3OD$) $\delta$: 2.00–2.07 (m, 4H, $CH_2$P, H-3), 2.85–2.95 (m, 3H, $CH_2$Ph, $H_{ax}$-4), 3.25 (ddt, 1H, $H_{eq}$-4, $^3J_{HH}$ 16.3 Hz, $^3J_{HH}$ 6.4 Hz, $^3J_{PH}$ 23.0 Hz), 4.17 (d, 1H, H-1, $^2J_{PH}$ 13.9 Hz), 6.92–7.33 (m, 14H, Ph and $C_6H_4$). $^{13}$C NMR (100.62 MHz, $CD_3OD$) $\delta$: 23.73 (d, $C^3$, $^1J_{PC}$ 64.0 Hz), 27.72 (d, $C^4$, $^2J_{PC}$ 4.6 Hz), 27.95 (d, $CH_2$Ph, $^2J_{PC}$ 3.5 Hz), 30.83 (d, $PCH_2$, $^1J_{PC}$ 65.2 Hz), 48.11 (d, $C^1$, $^1J_{PC}$ 58.7 Hz), 126.58 ($C^7$), 127.40 (*p*-C in $PhCH_2$), 127.60 ($C^5$), 127.64 ($C^6$), 128.35, 128.71 and 128.76 (*o*,*m*-C in $PhCH_2$, PhCHP), 128.97 (*p*-C in PhCHP), 130.37 (d, $C^8$, $^3J_{PC}$ 4.6 Hz), 130.55 (d, $C^9$, $^2J_{PC}$ 7.3 Hz), 134.98 (*i*-C in PhCH), 136.62 (d, $C^{10}$, $^3J_{PC}$ 10.4 Hz), 141.07 (d, *i*-C in $PhCH_2$, $^3J_{PC}$ 11.9 Hz). $^{31}$P NMR (161.98 MHz, $CD_3OD$) $\delta$: 42.20. IR (KBr, $\nu$/cm$^{-1}$): 3062, 3023, 2937, 2867, 1599, 1491, 1452, 1404, 1385, 1342, 1274, 1206, 1183, 1171, 1125, 1091, 1071, 1048, 1028, 938, 923, 894, 855, 781, 772, 742, 700, 672, 572, 521, 466. Found (%): C, 79.70; H, 6.68; P, 8.31. Calc. for $C_{23}H_{23}OP$ (%): C, 79.75; H, 6.69; P, 8.94.

*7*-tert-*Butyl-2-[2-(4*-tert-*butylphenyl)ethyl]-1-phenyl-1,2,3,4-tetrahydroisophosphinoline 2-oxide* **2b**: isolated yield 253 mg (55%), light yellow powder, mp 45 °C (hexane). $^1$H NMR (400.13 MHz, $CDCl_3$) $\delta$: 1.19, 1.28 (s, 18H, Me), 1.97–2.05 (m, 4H, $CH_2$P, H-3), 2.83–2.94 (m, 3H, $CH_2C_6H_4$, $H_{ax}$-4), 3.20–3.25 (m, 1H, $H_{eq}$-4), 4.15 (d, 1H, H-1, $^2J_{PH}$ 13.7 Hz), 7.13–7.5 (m, 12H, Ph, $C_6H_4$, $C_6H_3$). $^{13}$C NMR (100.62 MHz, $CDCl_3$) $\delta$: 23.23 and 23.35 (d, $C^3$,$^1J_{PC}$ 65.0 and 64.6 Hz), 26.99 and 27.49 (d, $C^4$, $^2J_{PC}$ 5.0 and 5.4 Hz), 27.72 and 27.76 (d, $CH_2C_6H_4$, $^2J_{PC}$ 3.8 and 4.2 Hz), 30.44 (d, $CH_2P$, $^1J_{PC}$ 64.8 Hz), 31.16 and 31.19 ($Me_3C$), 34.39 ($CMe_3$), 47.76 and 47.92 (d, $C^1$, $^1J_{PC}$ 57.4 Hz), 124.60 ($C^6$ in $C_6H_3$), 126.40 and 126.41 ($C_{c,c^1}$ in $C_6H_4$), 127.42 and 127.46 ($C_{b,b^1}$ in $C_6H_4$), 128.19 (d, $C^5$ in $C_6H_3$, $^4J_{PC}$ 3.8 Hz), 128.45 (*p*-C in Ph), 128.57 and 128.59 (*o*,*m*-C in Ph), 130.18 and 130.05 (d, $C^8$ in $C_6H_3$, $^3J_{PC}$ 4.5 Hz), 133.31 (d, *i*-C in Ph, $^2J_{PC}$ 10.8 Hz), 134.94 and 134.68 (d, $C^{10}$ in $C_6H_3$, $^3J_{PC}$ 5.4 Hz), 136.38 (d, $C^9$ in $C_6H_3$, $^2J_{PC}$ 10.7 Hz), 140.80 (d, $C_a$ in $C_6H_4$, $^3J_{PC}$ 12.2 Hz), 149.18 ($C_d$, in $C_6H_4$), 150.39 ($C^7$ in $C_6H_3$). $^{31}$P NMR (161.98 MHz, $CDCl_3$) $\delta$: 42.89. FT-IR (KBr, $\nu$/cm$^{-1}$): 3060, 3026, 2923, 2853, 1667, 1599, 1495, 1453, 1401, 1363, 1270, 1151, 1030, 944, 828, 745, 698, 569, 516. Found (%): C, 81.38; H, 8.23; P, 6.93. Calc. for $C_{31}H_{39}OP$ (%): C, 81.19; H, 8.57; P, 6.75.

*1-(4-Chlorophenyl)-2-(2-phenylethyl)-1,2,3,4-tetrahydroisophosphinoline 2-oxide* **2c**: isolated yield 210 mg (53%), light yellow powder, mp 43 °C (hexane). $^1$H NMR (400.13 MHz, $CDCl_3$) $\delta$: 1.98–2.03 (m, 4H, $CH_2$P, $C^3H_2$), 2.87–2.91 (m, 3H, $CH_2$Ph, $H_{ax}$-4), 3.17–3.27 (m, 1H, $H_{eq}$-4), 4.14 (d, 1H, H-1, $^1J_{PH}$ 13.8 Hz), 6.89–7.27 (m, 13H, Ph and $C_6H_4$). $^{13}$C NMR (100.62 MHz, $CDCl_3$) $\delta$: 23.74 (d, $C^3$, $^1J_{PC}$ 64.0 Hz), 27.74 (d, $C^4$, $^2J_{PC}$ 4.7 Hz), 27.98 (d, $CH_2$Ph, $^2J_{PC}$ 3.3 Hz), 30.86 (d, $CH_2$P, $^1J_{PC}$ 64.0 Hz), 48.15 (d, $C^1$, $^1J_{PC}$ 58.4 Hz), 126.60 ($C^7$), 127.42 (*p*-C, Ph), 127.60 ($C^5$), 127.66 ($C^6$), 128.37, 128.74 and 128.79 (*o*,*m*-C in Ph, $C_{b,b^1,c,c^1}$ in $C_6H_4$), 130.37 (d, $C^8$, $^3J_{PC}$ 4.6 Hz), 130.55 (d, $C^9$, $^2J_{PC}$ 7.3 Hz), 134.99 ($C_a$ in $C_6H_4$), 135.00 ($C_d$ in $C_6H_4$), 136.65 (d, $C^{10}$, $^3J_{PC}$ 10.73 Hz), 141.09 (d, *i*-C in Ph, $^3J_{PC}$ 11.8 Hz). $^{31}$P NMR (161.98 MHz, $CDCl_3$) $\delta$: 42.12. FT-IR ($\nu$/cm$^{-1}$): 3059, 3025, 2921, 2854, 1663, 1599, 1487, 1453, 1404, 1273, 1168, 1092, 1012, 935, 901, 864, 752, 701, 569, 520, 454. Found (%): C, 72.43; H, 5.80; P, 8.33. Calc. for $C_{23}H_{22}ClOP$ (%): C, 72.53; H, 5.82; P, 8.13.

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