Organic Syntheses

A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

# Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

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*These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.*

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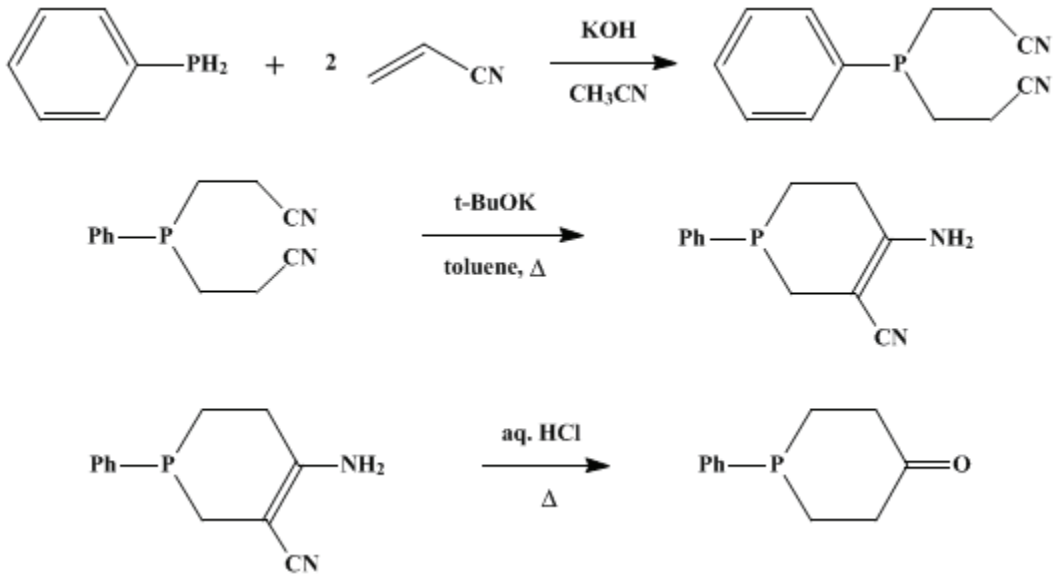
# 1-PHENYL-4-PHOSPHORINANONE

## [4-Phosphorinanone, 1-phenyl-]

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Checked by John R. Berry and Richard E. Benson.

## 1. Procedure

A. *Bis(2-cyanoethyl)phenylphosphine.* A 250-ml., three-necked flask is equipped with a magnetic stirrer, a thermometer, a pressure-equalizing dropping funnel, and a reflux condenser, with the entire system flushed with nitrogen. To the flask is added under an atmosphere of nitrogen 50.0 g. (0.454 mole) of phenylphosphine (Note 1), 50 ml. of acetonitrile, and 10 ml. of 10 *N* potassium hydroxide (Note 2). An ice-water bath is prepared for immediate cooling of the reaction flask. To the reaction mixture is added dropwise 50.0 g. (0.943 mole) of acrylonitrile (Note 3) with stirring and cooling over a period of 45–60 minutes. The rate of addition is controlled so that the temperature of the solution never exceeds 35° (Note 4). After the addition is complete, the solution is stirred at room temperature for an additional 2.5 hours. The reaction mixture is diluted with 100 ml. of ethanol and chilled to 0°. The product starts to crystallize, and the mixture is allowed to stand until crystallization is complete. The heavy slurry is filtered, and the crystalline product is washed with 200 ml. of cold ethanol and dried at 60° (2 mm.), yielding 74–84 g. (76–86%) of bis(2-cyanoethyl)phenylphosphine, m.p. 71–74° (Note 5). An additional 5–9 g. of product may be recovered from the combined washings and filtrate by concentration of the solution with subsequent chilling, bringing the total yield to 79–91 g. (80–93%).

B. 4-*Amino*-1,2,5,6-*tetrahydro*-1-*phenylphosphorin*-3-*carbonitrile.* A nitrogen-flushed, 1-l., three-necked flask equipped with a mechanical stirrer, a pressure-equalizing addition funnel, and a reflux condenser is charged with 25 g. (0.22 mole) of potassium *tert*-butoxide (Note 6) and 200 ml. of toluene (Note 7). The mixture is heated to reflux, and a solution of 43.2 g. (0.200 mole) of bis(2-cyanoethyl) phenylphosphine in 400 ml. of toluene is added dropwise with stirring over a period of 40–50 minutes (Note 8). After the addition is complete, the mixture is stirred and heated at reflux for an additional 3 hours. The mixture is cooled to room temperature, 250 ml. of water is added, and the resulting mixture is stirred for 30 minutes while the product is washed with two 50-ml. portions of cold ethanol and dried at 78° (1 mm.), yielding 36–38 g. (84–88%) of 4-amino-1,2,5,6-tetrahydro-1-phenylphosphorin-3-carbonitrile, m.p. 134.5–137° (Note 9). A small amount of product can be recovered from the filtrate (Note 10).

C. 1-*Phenyl*-4-*phosphorinanone.* A solution of 35 g. (0.16 mole) of 4-amino-1,2,5,6-tetrahydro-1-phenylphosphorin-3-carbonitrile in 400 ml. of 6 *N* hydrochloric acid is heated at a vigorous reflux under nitrogen for 30 hours in a 1-l., three-necked flask equipped with a mechanical stirrer and a reflux condenser (Note 11). The mixture is then cooled with an ice bath, and 300 ml. of cold 10 *N* potassium hydroxide is added with stirring over a period of 10 minutes (Note 12). The resulting solution is stirred an additional 10 minutes (Note 13) and extracted with 300 ml. of diethyl ether. The ether layer is separated and washed two times with 100-ml. portions of water, then dried. The solvent is removed by distillation using a rotary evaporator, and the resulting oil crystallizes on standing, giving 23–26 g. of crude product, m.p. 38–43°. Distillation through a short-path column yields 21.5–21.7 g. (68–69%) of pure 1-phenyl-4-phosphorinanone, m.p. 43.5–44°, b.p. 120–122° (0.02 mm.) (Note 14).

## 2. Notes

1. Phenylphosphine is available from Pressure Chemical Company and Strem Chemicals Inc., and best stored in a dry box under nitrogen. The compound is extremely air sensitive and malodorous. The container should be handled in the hood while wearing rubber gloves. Satisfactory preparations of phenylphosphine have been described.[2]
2. Potassium hydroxide solution is prepared by adding 5.6 g. of potassium hydroxide to sufficient water, giving a final volume of 10 ml.
3. Practical grade acetonitrile, available from Eastman Organic Chemicals, is satisfactory.
4. The optimum reaction temperature is approximately 30°. A yellow product results at higher reaction temperatures, while lower reaction temperatures lead to an uncontrollable reaction resulting from the base-initiated polymerization of acrylonitrile.
5. This product is of satisfactory purity for the next step. If a purer product is desired, bis(2-cyanoethyl) phenylphosphine may be recrystallized from hot ethanol or distilled, b.p. 215–223° (0.2 mm.).[3] The IR adsorption maxima (KBr), $cm.^{-1}$, occur at 3086, 2242, 1481, 1429, 1333, 750, 716, and 694. $^{1}H$ NMR spectrum ($CDCl_3$) shows complex multiplets centered at δ 7.2 (8H) and 7.6 (5H). The $^{31}P$ NMR spectrum (40.5 MHz, $C_2H_5OH$) has a signal at −21.4 p.p.m. relative to 85% phosphoric acid.
6. Potassium *tert*-butoxide is available from MSA Research Corp.
7. Reagent grade toluene was dried by standing over sodium ribbon.
8. The reaction mixture becomes quite viscous when the addition is about two-thirds complete.
9. The product, as isolated, is pure enough for conversion to 1-phenyl-4-phosphorinanone. If a higher degree of purity is desired, the product may be recrystallized from ethanol–water or chromatographed on alumina. IR absorption maxima (KBr), $cm^{-1}$ occur at 3401, 3344, 3236, 2874, 2169, 1642, 1603, 1399, 1323, 1188, 830, 781, 737, and 690. The $^{1}H$ NMR spectrum ($CDCl_3$, containing a small amount of dimethylsulfoxide-$d_6$) shows peaks at δ 1.8–3.0 (m, 2H), 5.15 (broad s, 2H), and 7.4–7.8 (m, 5H).
10. A small amount of product can be recovered from the filtrate by extracting the water layer with chloroform.
11. A white precipitate forms in the reaction medium after approximately 6 hours of reaction time. This precipitate may be the hydrochloride salt of 1-phenyl-4-phosphorinanone, m.p. >200°.
12. Rapid addition of base seems to result in higher yields than a more cautious addition, even though the temperature of the solution increases to about 40°. The solution must be strongly basic for efficient extraction.
13. Impure 1-phenyl-4-phosphorinanone may crystallize at this point. If crystallization occurs, the solid is recovered by filtration and washed thoroughly with two 20-ml. portions of water. The material is dried in a desiccator over phosphorus pentoxide, giving a product of m.p. 42.5–44°. To obtain a product satisfactory for distillation, the checkers found it necessary to dissolve the material in ether and wash it with water before distillation.
14. GC analysis of the product on a column containing 10% SE-30 on acid-washed Chromosorb U indicated one component, injected as a 20% solution in ethanol at 230° and helium flow of 15 ml. per minute with a retention time of 760 seconds. The $^{1}H$ NMR spectrum ($CDCl_3$) shows multiplets centered at δ 2.4 (8H) and 7.4 (5H). IR absorption maxima (KBr), $cm^{-1}$, occur at 3077 (=CH), 2976 and 2924 (CH), 1704 (C=O), 1595 and 1486 (aromatic C=C), 1433 (P-phenyl), 754 and 701 (monosubstituted phenyl). The $^{31}P$ NMR spectrum (40.5 MHz., $CHCl_3$) shows a signal at −39.3 p.p.m. relative to 85% phosphoric acid.

## 3. Discussion

This reaction sequence illustrates a broadly applicable synthetic route to a functionalized phosphorus heterocycle and has been utilized for the synthesis of 1-phenyl-,[4,5] 1-ethyl-,[4] and 1-methyl-4-phosphorinanone.[6]

The cyanoethylation of phenylphosphine has been carried out in the presence of a basic catalyst,[3] and at high temperature.[7,8] (2-Cyanoethyl)phenylphosphine has been reported as a contaminant but this difficulty has not been observed in the procedure reported herein.

The intermediates, bis(2-cyanoethyl)phenylphosphine and 4-amino-1,2,5,6-tetrahydro-1-phenylphosphorin-3-carbonitrile, are easily isolated and characterized, and show little or no oxidation when exposed to the air. 1-Phenyl-4-phosphorinanone is a highly-crystalline material, more sensitive to air oxidation than its two precursors. However, 1-phenyl-4-phosphorinanone may be stored in a well-capped bottle for several months without appreciable oxidation. It is best stored in a dark bottle in a dry box under nitrogen.

An extension of this type of synthetic sequence is illustrated by the cyclization of 2-cyanoethyl(2-cyanophenyl)phenylphosphine to the corresponding 2-enaminenitrile followed by hydrolysis with acid, yielding 2,3-dihydro-1-phenyl-4(1*H*)phosphinolinone.[9] The only other reported synthesis of this class of compounds involves the addition of phenylphosphine to substituted divinyl ketones.[10,11]

Phosphorinanones have been utilized as substrates for the preparation of alkenes,[12] amines,[13] indoles,[5,14] and in the synthesis of a series of secondary and tertiary alcohols *via* reduction,[10] and by reaction with Grignard[6,12] and Reformatsky[12,15] reagents. Phosphorinanones have also been used as precursors to a series of 1,4-disubstituted phosphorins.[16] The use of 4-amino-1,2,5,6-tetrahydro-1-phenylphosphorin-3-carbonitrile for the direct formation of phosphorino[4,3-*d*] pyrimidines has been reported.[17] The $^{13}C$ NMR spectra of 1-phenylphosphorinanone has been reported.[18]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 9, 362

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## References and Notes


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## Appendix
## Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

ether,
diethyl ether (60-29-7)

acetonitrile (75-05-8)

chloroform (67-66-3)

PHOSPHORUS (7723-14-0)

nitrogen (7727-37-9)

potassium hydroxide (1310-58-3)

toluene (108-88-3)

sodium (13966-32-0)

acrylonitrile (107-13-1)

helium (7440-59-7)

phenylphosphine (638-21-1)

1-Phenyl-4-phosphorinanone,
4-Phosphorinanone, 1-phenyl- (23855-87-0)

bis(2-cyanoethyl)phenylphosphine (15909-92-9)

4-Amino-1,2,5,6-tetrahydro-1-phenylphosphorin-3-carbonitrile (84819-76-1)

1-methyl-4-phosphorinanone

(2-Cyanoethyl)phenylphosphine

2-cyanoethyl(2-cyanophenyl)phenylphosphine

phosphorus pentoxide (1314-56-3)

potassium tert-butoxide (865-47-4)

2,3-dihydro-1-phenyl-4(1H)phosphinolinone