



A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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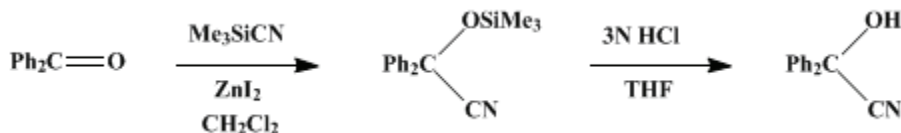
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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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CONVERSION OF KETONES TO CYANOHYDRINS: BENZOPHENONE CYANOHYDRIN

[Benzeneacetonitrile, α -hydroxy-*o*-phenyl]



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Checked by Tod Holler and George Büchi.

1. Procedure

A. *O*-(Trimethylsilyl)benzophenone cyanohydrin. A 250-mL, one-necked flask equipped with a reflux condenser, magnetic stirring bar, and drying tube is charged with 22.0 g (0.12 mol) of benzophenone (Note 1), 13.9 g (0.14 mol) of trimethylsilyl cyanide (Note 2), 600 mg (1.9 mmol) of anhydrous zinc iodide (Note 3), and 50 mL of dry methylene chloride (Note 4). The solution is heated at 65°C in an oil bath for 2 hr (Note 5) and (Note 6). The solvent is removed on a rotary evaporator to yield 36.4–37.9 g of crude product (Note 7), which is used in the next step without purification (Note 8).

B. Benzophenone cyanohydrin. To the 250-mL flask, which contains the crude *O*-(trimethylsilyl)benzophenone cyanohydrin, is added 50 mL of tetrahydrofuran (Note 9) and 30 mL of 3 *N* hydrochloric acid. The mixture is heated at 65°C (oil bath temperature) for 1 hr. The solution is poured into a separatory funnel and 30 mL of water is added. The aqueous phase is separated and back-extracted with three 100-mL portions of diethyl ether. The ethereal extracts are combined with the tetrahydrofuran solution and dried over anhydrous magnesium sulfate, filtered, and solvent is removed by evaporation on a rotary evaporator to give a yellow solid. The material is recrystallized from 300 mL of toluene and dried at a pressure of 0.05 mm overnight to give 17.7–18.8 g of white crystals. Concentration of the mother liquors to 100 mL produced a second crop of 1.1–3.8 g for a combined yield of 17.9–21.5 g (79–86%), mp 127–130°C (Note 10).

2. Notes

1. Benzophenone was purchased from Distillation Products (Eastman Organic Chemicals) and used without purification.
2. Trimethylsilyl cyanide was prepared shortly before use according to the procedure of Livinghouse, T. *Org. Synth. Coll. Vol. VII 1990*, 517.
3. Anhydrous zinc iodide was purchased from Alfa Products, Ventron Corporation, and used without further purification.
4. The use of this solvent is optional. The reaction can be carried out in the absence of solvent without significant change in yield. For certain unhindered ketones the solvent is helpful in dissipating the heat generated in the reaction.
5. For certain unhindered ketones external cooling may be necessary instead of heating due to the exothermicity of the reaction.
6. The checkers followed the reaction by IR spectroscopy and found that the benzophenone carbonyl peak (1640 cm⁻¹) disappeared after 2 hr.
7. If purification is desired, it may be achieved by vacuum distillation of this crude product, bp 104°C (0.5 mm).
8. On prolonged standing the crude product appears to undergo some decomposition. Thus it should be used directly in the next step for maximum yield.
9. For many analogs the use of solvent and/or heating is not necessary. However, both solvent and heating are necessary for hindered cyanohydrins, such as the one described in this procedure.

10. The submitters report a melting point of 131–132.5°C. The melting point has been previously reported to be 127–130°C.²

3. Discussion

Traditionally cyanohydrins have been prepared by processes that require the establishment of an equilibrium between a ketone and its corresponding cyanohydrin. For many ketones, especially those that are sterically hindered, the position of the equilibrium is unsatisfactory for the effective synthesis of the cyanohydrin. We describe herein a general method for the synthesis of cyanohydrins that does not depend on an equilibrium process. As a result this synthetic procedure can be used to convert a wide variety of dialkyl, diaryl, and arylalkyl ketones into their corresponding cyanohydrins. In addition to the described conversion of benzophenone into its cyanohydrin, acetophenone, fluorenone, *tert*-butyl phenyl ketone, and a wide variety of aliphatic ketones have been converted into cyanohydrins by this general procedure (Table I).³

O-(Trimethylsilyl) benzophenone cyanohydrin has been prepared previously by the addition of trimethylsilyl cyanide to benzophenone using an aluminum chloride catalyst.⁴ The preparation of cyanohydrin silyl ethers described in the synthesis is based on the general procedure of Evans, Carroll, and Truesdale.⁵ Trimethylsilyl cyanide has been prepared also by Zubrick, Dunbar, and Durst.⁶ The overall procedure is that of Gassman and Talley.³

Benzophenone cyanohydrin has been synthesized previously by the nitrogen dioxide oxidation of 1,2-dicyanotetraphenylethane.²

TABLE I
PREPARATION OF CYANOHYDRINS

Yield	Product (%)	mp [bp] (°C)
Cyclohexanone cyanohydrin	90	27–28 [63° (10 ⁻⁶ mm)]
Cyclooctanone cyanohydrin	93	115–116
Fluorenone cyanohydrin	98	118.5–120
<i>tert</i> -Butyl phenyl ketone cyanohydrin	99	82–83
<i>p</i> -Chloroacetophenone cyanohydrin	94	91.5–92.5
<i>p</i> -Nitroacetophenone cyanohydrin	89	112–113
<i>p</i> -Acetylbenzotrile cyanohydrin	95	77.5–78.5
<i>p</i> -Methoxyacetophenone cyanohydrin	96	78–80
<i>p</i> -Methylacetophenone cyanohydrin	97	79.5–80

References and Notes

1. Department of Chemistry, University of Minnesota, Minneapolis, MN 55455.
2. Wittig, G.; Pockels, U. *Chem. Ber.* **1936**, *69*, 790–792.
3. Gassman, P. G.; Talley, J. J. *Tetrahedron Lett.* **1978**, 3773–3776.
4. Liddy, W.; Sundermeyer, W. *Chem. Ber.* **1973**, *106*, 587–593.
5. Evans D. A.; Carroll, G. L.; Truesdale, L. K. *J. Org. Chem.* **1974**, *39*, 914–917.
6. Zubrick, J. W.; Dunbar, B. I.; Durst, H. D. *Tetrahedron Lett.* **1975**, 71–74.

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

BENZOPHENONE CYCANOHYDRIN

hydrochloric acid (7647-01-0)

diethyl ether (60-29-7)

Acetophenone (98-86-2)

aluminum chloride (3495-54-3)

toluene (108-88-3)

Benzophenone (119-61-9)

nitrogen dioxide (10102-44-0)

methylene chloride (75-09-2)

magnesium sulfate (7487-88-9)

Tetrahydrofuran (109-99-9)

fluorenone (486-25-9)

cyclohexanone cyanohydrin (931-97-5)

zinc iodide

Trimethylsilyl cyanide (7677-24-9)

tert-Butyl phenyl ketone (938-16-9)

Benzeneacetonitrile, α -hydroxy- α phenyl,
Benzophenone cyanohydrin (4746-48-9)

1,2-dicyanotetraphenylethane

Cyclooctanone cyanohydrin

Fluorenone cyanohydrin

O-(trimethylsilyl) benzophenone cyanohydrin,
O-(Trimethylsilyl)benzophenone cyanohydrin (40326-25-8)

tert-Butyl phenyl ketone cyanohydrin

p-Chloroacetophenone cyanohydrin

p-Nitroacetophenone cyanohydrin

p-Acetylbenzonitrile cyanohydrin

p-Methoxyacetophenone cyanohydrin

p-Methylacetophenone cyanohydrin

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