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Working with Hazardous Chemicals

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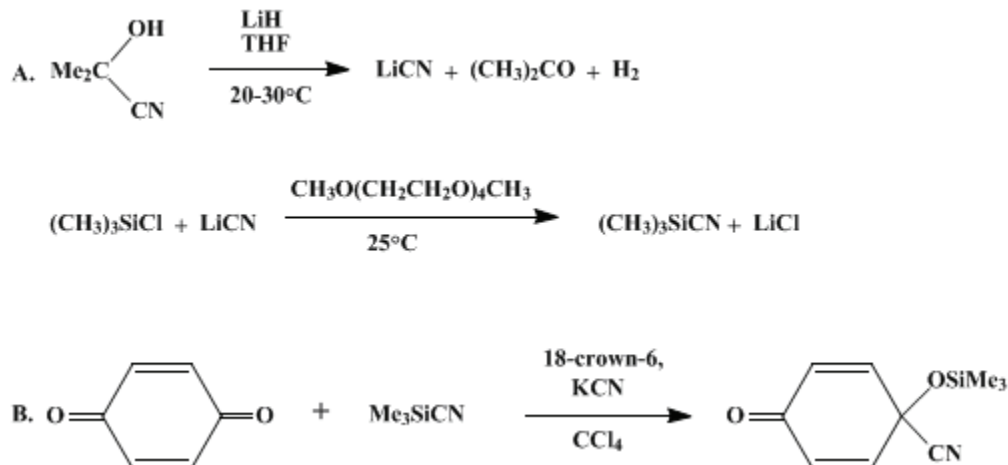
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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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TRIMETHYLSILYL CYANIDE: CYANOSILATION OF *p*-BENZOQUINONE

[Silanecarbonitrile, trimethyl]

A. $Me_2C\overset{OH}{\underset{CN}{}} \xrightarrow[\text{20-30°C}]{\substack{\text{LiH} \\ \text{THF}}} LiCN + (CH_3)_2CO + H_2$

$(CH_3)_3SiCl + LiCN \xrightarrow[\text{25°C}]{CH_3O(CH_2CH_2O)_4CH_3} (CH_3)_3SiCN + LiCl$

B. [p-benzoquinone] $+ Me_3SiCN \xrightarrow[\text{CCl}_4]{\substack{\text{18-crown-6,} \\ \text{KCN}}}$ [product with OSiMe₃ and CN]

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1. Procedure

Caution! Trimethylsilyl cyanide is very toxic. All reactions in this sequence should be carried out in a hood.

A. *Trimethylsilyl cyanide.* A 1-L, round-bottomed flask equipped with a magnetic stirrer, nitrogen inlet, and a 60-mL addition funnel is charged with 5.0 g (0.624 mol) of lithium hydride (Note 1) and 500 mL of anhydrous tetrahydrofuran (Note 2). The stirred suspension is cooled in an ice bath and 42.6 g of acetone cyanohydrin (45.7 mL, 0.501 mol) (Note 3) is added dropwise over 15 min. After the addition is complete, the ice bath is removed and the mixture stirred for 2 hr at room temperature (Note 4). The magnetic stirring bar is removed and the solvent evaporated as completely as possible on a rotary evaporator. The white lithium cyanide is then dried in vacuo for 3 hr (Note 5) and (Note 6). The lithium cyanide is freed from the sides of the flask and broken up with a spatula (Note 7). A 250-mL round-bottomed flask equipped with an ice bath, magnetic stirrer, thermometer, and nitrogen inlet is charged with 54.32 g (63.46 ml, 0.500 mol) of trimethylchlorosilane (Note 8) and 100 mL of bis[2-(2-methoxyethoxy)ethyl] ether (Note 9). The lithium cyanide is added to this stirred solution over 15 min through Gooch tubing (Note 10). After the addition is complete, the ice bath is removed and the milky suspension stirred overnight at room temperature. The Gooch tubing and the thermometer are then removed from the reaction flask and a stillhead equipped for downward vacuum distillation is attached. A 100-mL, round-bottomed flask immersed halfway in an acetone-dry ice slush bath (Note 11) is employed as the receiver. The volatile compounds are distilled under a pressure of 50 mm (bp 25–55°C) by heating the contents of the pot using an oil bath (Note 12). The distillate is carefully redistilled through a well-insulated 15-cm column packed with glass helices under an inert atmosphere. A 25–40 mL forerun (bp 66–113°C), consisting primarily of tetrahydrofuran and hexamethyldisiloxane, is first collected. The second fraction, containing 29–41 g (59–82%) of trimethylsilyl cyanide, bp 114–117°C, n_D^{25} 1.3902 (Note 13), then distills. A purity of ca. 97% was established by GC analysis (Note 14) and (Note 15); the product is suitable for synthetic use without further purification.

B. *Cyanosilylation of p-benzoquinone.* A 100-mL, round-bottomed flask equipped with a magnetic stirrer, West condenser, and a nitrogen inlet is charged with 6.30 g (58.2 mmol) of p-benzoquinone

(Note 16), 10 mL of dry carbon tetrachloride, and 8 mL (63.03 mmol) of trimethylsilyl cyanide. The stirred suspension is heated to a gentle reflux by means of a heat gun to dissolve all the *p*-benzoquinone. It is then allowed to cool slowly until the crystallization of the *p*-benzoquinone starts (Note 17), at which time 5 mg of the 1 : 1 complex between potassium cyanide and 18-*crown*-6 (Note 18) is added through the top of the condenser. An immediate vigorous reflux sets in and continues for 1–2 min (Note 19). The stirred reaction mixture is permitted to cool slowly to room temperature, whereupon the condenser is removed and 3 g of Florisil (Note 20) is added. After stirring for an additional 15 min, 10 mL of dry carbon tetrachloride is added. The suspension is then filtered and the filtercake leached with three 5-mL portions of carbon tetrachloride. The solvent is evaporated from the filtrate as completely as possible on a rotary evaporator, at which point crystallization of the residue usually begins (Note 21). The last traces of solvent and trimethylsilyl cyanide are then removed in vacuo over 20 hr at 50 μ to afford 12.0–12.2 g of crude product. The trimethylsilyl cyanohydrin is recrystallized by dissolving the crude material in 25 mL of hot hexane and allowing the resulting solution to cool slowly to room temperature (Note 22). After collection by filtration the product is rinsed with two 5-mL portions of hexane and airdried to yield 7.54–9.77 g (63%–81%) of white to buff-colored needles, mp 65–67°C (Note 23) and (Note 24).

2. Notes

1. Commercial lithium hydride (Alfa Products, Morton Thiokol, Inc.) was used.
2. Commercial tetrahydrofuran was distilled from sodium benzophenone ketyl immediately before use.
3. Commercial acetone cyanohydrin (Aldrich Chemical Company, Inc.) was used without further purification.
4. A vigorous evolution of hydrogen gas occurs during the addition of the acetone cyanohydrin. Hydrogen evolution virtually ceases after stirring at room temperature for 2 hr.
5. It is essential to exclude atmospheric moisture as much as possible during this operation.
6. A small quantity of tetrahydrofuran remains complexed in the solid lithium cyanide and is separated later in the preparation.
7. This operation must be performed rapidly to avoid water absorption by the hygroscopic lithium cyanide.
8. Commercial trimethylchlorosilane (Silar Laboratories, Inc.) was distilled from calcium hydride immediately before use.
9. Commercial bis[2-(2-methoxyethoxy)ethyl] ether, "tetraglyme" (Eastman Organic Chemicals), was dried over Linde 4A molecular sieves for 24 hr before use.
10. The internal temperature is maintained at or below 35°C during this operation by periodic cooling with an ice bath.
11. Trimethylsilyl cyanide solidifies in the receiver during the course of the distillation. *It is absolutely necessary that the receiver be immersed no more than halfway in the slush bath.* Further immersion may cause the product to solidify in the end of the condenser. This necessitates cessation of the distillation to unclog the apparatus.
12. The temperature of the oil bath is raised from 25 to 110°C over 45 min and then maintained at the upper temperature until no more product distills.
13. The product exhibits the following properties: ^{1}H NMR (CCl$_4$ with CHCl$_3$ internal standard) δ: 0.4 [s, Si(CH$_3$)$_3$]; IR (neat) cm^{-1}: 2200 (-CN).
14. The GC analysis was performed on an 8-ft column packed with 5% OV-17 on Anachrome ABS.
15. Trimethylsilyl cyanide hydrolyzes rapidly in moist air and is best stored under an inert atmosphere.
16. Commercial *p*-benzoquinone (Matheson, Coleman, and Bell, Inc.) was recrystallized from 95% ethanol before use.
17. The initiation of crystallization indicates the optimum reaction temperature for the catalyzed cyanosilylation of *p*-benzoquinone. The use of higher temperatures results in excessive darkening of the product and a decrease in yield.
18. The 1 : 1 complex is conveniently prepared by dissolving 0.652 g (10 mmol) of pulverized potassium cyanide and 2.640 g (10 mmol) of commercial 18-*crown*-6 (Aldrich Chemical Company, Inc.) in 45 mL of anhydrous methanol by swirling and warming. The methanol is then evaporated at a rotary evaporator and the white complex dried in vacuo over night.
19. *Caution! Extreme care must be taken during the addition of the catalyst. The addition of too much catalyst or the use of higher reaction temperatures may result in the reaction mixture boiling over.*

20. Florisil obtained from Matheson, Coleman, and Bell, Inc. was used.
21. Crystallization of the residue may also be induced by the addition of a seed crystal or scratching with glass rod.
22. In some instances addition of a seed crystal during cooling is necessary.
23. *p*-Benzoquinone monotrimethylsilyl cyanohydrin darkens on prolonged exposure to light and air. It is best stored under nitrogen in the dark.
24. An analytically pure sample, mp 67–67.5°C, may be obtained by a second recrystallization from cyclohexane: ^{1}H NMR (CCl$_4$) δ: 0.30 (s, 9, CH$_3$), 6.30 (d, 1, J = 10, C=CH), 6.83 (d, 1, J = 10, C=CH); IR (CCl$_4$) cm^{-1}: 1678 (C=O), 1252, 845 (Si-CH$_3$).

3. Discussion

Trimethylsilyl cyanide is a useful reagent for the preparation of β-amino alcohols,[6] α-amino nitriles,[2] and α-trimethylsiloxyacrylonitriles[3] from the corresponding ketones, imines, and ketenes. The reagent adds rapidly to the carbonyl of aldehydes at 25°C,[6] and the resulting adducts have proved useful precursors for the preparation of carbonyl anion synthons.[4] Enones give exclusively the products derived from 1,2-addition.[6]

Trimethylsilyl cyanide has been prepared in modest yield by the action of hexamethyldisilazane on hydrogen cyanide[5] and the reaction of silver cyanide with trimethylchlorosilane.[5,7] It has been prepared in good yield by the treatment of preformed lithium cyanide (from LiH and HCN) with trimethylchlorosilane in ether.[7] The procedure described here not only affords trimethylsilyl cyanide in good yield, but also avoids the use of hydrogen cyanide and the need for Schlenk ware.

Table I illustrates the cyanosilylation of several representative ketones and aldehydes.

TABLE 1
CYANOSILYLATION OF KETONES AND ALDEHYDES

Substrate	Silylcyanohydrin	Yield (%)	Ref.
Benzophenone	(78)^a	98	6
Crotonaldehyde	(88)^a	98	6
Furfural		99	6
Cyclooctanone		94	7
Cyclododecanone		94	7
Camphor		>95^b	7
α-Tetralone		>95^b	7
3-Methyl-3-penten-2-one		91	7

^{a} No catalyst employed; zinc iodide catalyst used in all other cases.
^{b} Yield determined by GLC analysis.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 7, 20
- Org. Syn. Coll. Vol. 7, 294

References and Notes

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

sodium benzophenone ketyl

Florisil

ethanol (64-17-5)

methanol (67-56-1)

ether (60-29-7)

hydrogen (1333-74-0)

hydrogen cyanide (74-90-8)

carbon tetrachloride (56-23-5)

nitrogen (7727-37-9)

potassium cyanide (151-50-8)

cyclohexane (110-82-7)

Benzophenone (119-61-9)

Furfural (98-01-1)

p-benzoquinone (106-51-4)

Acetone cyanohydrin (75-86-5)

camphor (21368-68-3)

Tetrahydrofuran (109-99-9)

α-Tetralone (529-34-0)

silver cyanide (506-64-9)

hexane (110-54-3)

crotonaldehyde (123-73-9)

calcium hydride (7789-78-8)

zinc iodide

Cyclooctanone (502-49-8)

cyclododecanone (830-13-7)

lithium hydride (7580-67-8)

Trimethylsilyl cyanide,
Silanecarbonitrile, trimethyl (7677-24-9)

trimethylchlorosilane (75-77-4)

hexamethyldisiloxane (107-46-0)

lithium cyanide

bis[2-(2-methoxyethoxy)ethyl] ether (143-24-8)

3-Methyl-3-penten-2-one

hexamethyldisilazane (999-97-3)

p-Benzoquinone monotrimethylsilyl cyanohydrin (40861-57-2)