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of Reliable Methods
for the Preparation
of Organic Compounds

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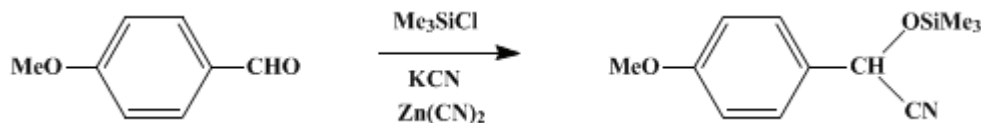
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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

Organic Syntheses, Coll. Vol. 7, p.521 (1990); Vol. 62, p.196 (1984).

in situ CYANOSILYLATION OF CARBONYL COMPOUNDS: *O*-TRIMETHYLSILYL-4-METHOXYMANDELONITRILE

[Benzeneacetonitrile, 4-methoxy- α -[(trimethylsilyl)oxy]-]



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1. Procedure

Caution! Potassium cyanide is highly toxic. Care should be taken to avoid direct contact of the chemical or its solutions with the skin, and impervious gloves should be worn to handle the reagent.

In a 1-L, three-necked, round-bottomed flask equipped with a mechanical stirrer, a reflux condenser fitted with a nitrogen-inlet tube, and a rubber septum (Note 1) are placed 97.5 g (1.5 mol) of finely ground potassium cyanide (Note 2), 81.4 g (0.75 mol, 95.2 mL) of chlorotrimethylsilane (Note 3), 68 g (0.5 mol) of *p*-anisaldehyde (Note 4), 100 mL of dry acetonitrile (Note 5), and 0.5 g (4.25 mmol) of zinc cyanide (Note 6). The reaction mixture is blanketed with dry nitrogen (Note 7), stirring is begun, and the temperature is raised (heating mantle) to maintain gentle reflux. Heating is continued under these conditions for 30 hr (Note 8), with the occasional removal of small samples by syringe for monitoring by GLC (Note 9). On completion of the reaction, the mixture is cooled to ambient temperature and filtered. The filtercake is washed twice with 50 mL of dry acetonitrile and the combined filtrates are concentrated on a rotary evaporator. The residue is distilled at reduced pressure (Note 10). The yield of the colorless liquid (Note 10), which boils at 93–98°C (0.15 mm), amounts to 105–115 g (90–98% based on *p*-anisaldehyde).

2. Notes

- All glassware was oven-dried overnight at 130°C, assembled hot, and allowed to cool under a flow of dry nitrogen.
- Reagent-grade potassium cyanide was purchased from Matheson, Coleman and Bell, and dried at 115°C (0.5 mm) for 24 hr. The checkers found it necessary to use newly purchased potassium cyanide. The use of potassium cyanide which was several years old gave incomplete reaction even at extended reaction times. The large excess of potassium cyanide is used simply to obtain convenient reaction times. For comparison, use of 1.5 equiv of KCN gave 38% conversion under conditions where 3 equiv produced 100% conversion.
- Chlorotrimethylsilane was supplied by Petrarch Systems, Inc. and used without further purification.
- p*-Anisaldehyde (4-methoxybenzaldehyde), 95%, was used as supplied by Aldrich Chemical Co.
- Acetonitrile, 99%, supplied by Aldrich Chemical Co., was dried over Linde 4A molecular sieves for 12 hr and decanted.
- Technical-grade zinc cyanide was used as supplied by MCB, Inc. Other Lewis acids, notably aluminum chloride, zinc bromide, and zinc iodide, may be used as catalysts for the reaction.
- To "blanket with nitrogen," the checkers simply prepared the reaction mixture with the flask open, introduced a flow of nitrogen over the surface for a few minutes, and then closed the system with an exit through a mercury bubbler to maintain a positive pressure.
- The reaction time required depends on the catalyst. Zinc iodide, zinc cyanide, and zinc bromide produce essentially complete conversion under these conditions in approximately 16.5, 28, and 30 hr, respectively, probably reflecting solubility differences. When zinc iodide is used, the distilled product is often colored because of the formation of small amounts of iodine.
- This may be done using a simple boiling-point column. We have employed either 10% UCW-98 on

Chromasorb W or SP-2100 on 80/100 Supelcoport G2642. The checkers did not monitor the reaction except to extract a small sample after 30 hr in order to verify the absence of starting aldehyde by ^1H NMR spectroscopy.

10. Distillation should be below 100°C . In some instances, at distillation temperatures in excess of 100°C , reversion to the starting aldehyde and trimethylsilyl cyanide has been observed. The pure compound shows the following spectral data: ^1H NMR (CCl_4): δ 0.28 (s, 9 H), 3.86 (s, 3 H), 5.35 (s, 1 H), 6.83 (d, $J = 9, 2$ H), 7.35 (d, $J = 9, 2$ H); IR (film) cm^{-1} : 2965, 1614, 1512, 1258, 1180, 1089, 878, 850. The purity of the crude product is generally such that a distillation forecut need not be taken.

3. Discussion

Cyanosilylations have generally been accomplished by addition of a trialkylsilyl cyanide to the corresponding aldehyde or ketone.^{2,3,4,5} Although this method is straight-forward and proceeds in good to excellent yield, use of preformed trialkylsilyl cyanides has a number of disadvantages, particularly when one considers larger-scale preparations. Trialkylsilyl cyanides can be prepared⁶ by treatment of the corresponding silyl chlorides with either silver cyanide or lithium cyanide generated in situ by reaction of lithium hydride with hydrogen cyanide. The former procedure involves the use of stoichiometric quantities of a rather expensive reagent, while the latter involves handling fairly large quantities of hydrogen cyanide gas. In addition, both procedures require relatively long reaction times and distillation of the silyl cyanide, and produce only moderate to good yields. More recently, improved syntheses of trimethylsilyl cyanide have appeared.^{7,8} Commercially available trimethylsilyl cyanide is also rather expensive.

Silylated cyanohydrins have also been prepared via silylation of cyanohydrins themselves⁹ and by the addition of hydrogen cyanide to silyl enol ethers.¹⁰ Silylated cyanohydrins have proved to be quite useful in a variety of synthetic transformations, including the regiospecific protection of *p*-quinones,¹¹ as intermediates in an efficient synthesis of α -aminomethyl alcohols,⁶ and for the preparation of ketone cyanohydrins themselves.¹² The silylated cyanohydrins of heteroaromatic aldehydes have found extensive use as acyl anion equivalents, providing general syntheses of ketones¹³ and acyloins.¹⁴ Acyloins are also readily prepared via addition of Grignard reagents to silylated cyanohydrins followed by hydrolysis of the magnesium imine intermediate.¹⁵ Alternatively, reduction of this same intermediate with borohydride provides a general synthesis of aminoalcohols.¹⁶ Tetric acids may be produced on reaction of silylated cyanohydrins with Reformatsky reagents.¹⁷

The in situ cyanosilylation of *p*-anisaldehyde is only one example of the reaction that can be applied to aldehydes and ketones in general.¹⁸ The simplicity of this one-pot procedure, coupled with the use of inexpensive reagents, are important advantages over previous methods. The silylated cyanohydrins shown in Table I were prepared under conditions similar to those described here. Enolizable ketones and aldehydes have a tendency to produce silyl enol ethers as by-products in addition to the desired cyanohydrins. The problem can be overcome by using a modified procedure in which dimethylformamide is employed as solvent.¹⁸

TABLE I
IN SITU CYANOSILYLATION OF CARBONYL COMPOUNDS

$\begin{array}{c} \text{OSi(CH}_3\text{)}_3 \\ \\ \text{R}^1\text{-C-R}^2 \\ \\ \text{CN} \end{array}$	Distilled Yield (%)bp ($^\circ\text{C}$) (pressure, mm)	
$\text{R}^1 = \text{C}_6\text{H}_5, \text{R}^2 = \text{H}$	95–98	93–95 (1.75)
$\begin{array}{c} \text{OSi(CH}_3\text{)}_3 \\ \\ \text{C}_6\text{H}_5\text{-C-H} \\ \\ \text{CN} \end{array}$		
$\text{R}^1 = 4\text{-CH}_3\text{C}_6\text{H}_4, \text{R}^2 = \text{H}$		

$\begin{array}{c} \text{OSi(CH}_3\text{)}_3 \\ \\ 4\text{-CH}_3\text{C}_6\text{H}_4\text{-C-H} \\ \\ \text{CN} \end{array}$	91	87 (0.45)
$R^1 = 2\text{-ClC}_6\text{H}_4, R^2 = \text{H}$		
$\begin{array}{c} \text{OSi(CH}_3\text{)}_3 \\ \\ 2\text{-ClC}_3\text{H}_4\text{-C-H} \\ \\ \text{CN} \end{array}$	99	92–93 (0.45)
$R^1 = 4\text{-ClC}_6\text{H}_4, R^2 = \text{H}$		
$\begin{array}{c} \text{OSi(CH}_3\text{)}_3 \\ \\ 4\text{-ClC}_6\text{H}_4\text{-C-H} \\ \\ \text{CN} \end{array}$	93	100 (0.45)
$R^1 = \text{C}_6\text{H}_5, R^2 = \text{CH}_3$		
$\begin{array}{c} \text{OSi(CH}_3\text{)}_3 \\ \\ \text{C}_6\text{H}_5\text{-C-CH}_3 \\ \\ \text{CN} \end{array}$	93	73–75 (0.9)
$R^1, R^2 = (-\text{CH}_2-)_5$		
$\begin{array}{c} \text{OSi(CH}_3\text{)}_3 \\ \\ \text{-(CH}_2\text{)}_5\text{-C-(CH}_2\text{)}_5\text{-} \\ \\ \text{CN} \end{array}$	89	96 (15)
$R^1 = c\text{-C}_6\text{H}_{11}, R^2 = \text{H}$		
$\begin{array}{c} \text{OSi(CH}_3\text{)}_3 \\ \\ c\text{-C}_6\text{H}_{11}\text{-C-H} \\ \\ \text{CN} \end{array}$	87	106–108 (6.5)

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

tremethylsilyl cyanide

acetonitrile (75-05-8)

hydrogen cyanide (74-90-8)

nitrogen (7727-37-9)

potassium cyanide (151-50-8)

iodine (7553-56-2)

aluminum chloride (3495-54-3)

dimethylformamide (68-12-2)

silver cyanide (506-64-9)

zinc bromide (7699-45-8)

zinc cyanide (557-21-1)

zinc iodide

lithium hydride (7580-67-8)

Trimethylsilyl cyanide (7677-24-9)

CHLOROTRIMETHYLSILANE (75-77-4)

lithium cyanide

Benzeneacetonitrile, 4-methoxy- α -[(trimethylsilyl)oxy]- (66985-48-6)

4-methoxybenzaldehyde,
p-anisaldehyde (123-11-5)

silyl cyanide

O-Trimethylsilyl-4-methoxymandelonitrile