Tributyltin Cyanide-Catalyzed Addition of Triethylsilyl Cyanide to Aldehydes†

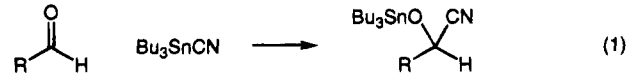
Matthias Scholl[1] and Gregory C. Fu*

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

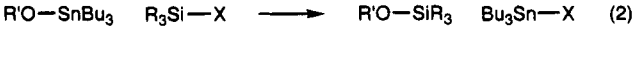
Received September 7, 1994

Because cyanohydrins serve as useful precursors to many important classes of organic compounds (e.g., β-amino alcohols, α-hydroxy aldehydes, and α-hydroxy acids), considerable energy has been devoted to designing efficient methods for their synthesis.[2] As part of a broader program directed toward the development of organotin reagents for stereoselective organic synthesis, we report in this Note a new, Bu_3SnCN-catalyzed method for generating silylated cyanohydrins from aldehydes.

Two key observations provided the basis for our study: (1) tributyltin cyanide adds to aldehydes (eq 1) much more rapidly than does trimethylsilyl cyanide,[3] and (2) the silylation of tin alkoxides by silyl halides is a facile process (eq 2).[4,5] In light of this work, we anticipated that



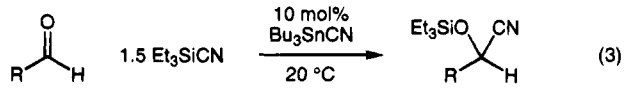
(1)



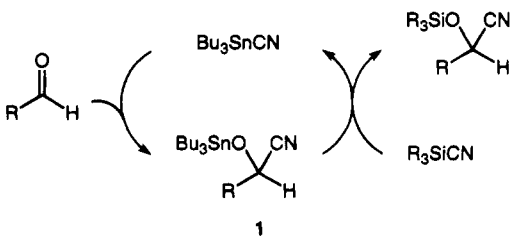
(2)

tin cyanides would serve as effective *catalysts* for the cyanosilylation of carbonyl groups[6,7] (Figure 1). Thus, Bu_3SnCN would add to an aldehyde to produce a stannylated cyanohydrin (**1**), which would then undergo silylation by R_3SiCN to afford a silylated cyanohydrin and to regenerate the Bu_3SnCN catalyst.

We have found that tributyltin cyanide does indeed catalyze the cyanosilylation of carbonyl groups. Thus, treatment of a variety of aldehydes with 10 mol % Bu_3SnCN and 1.5 equiv of Et_3SiCN[8] neat at room temperature affords the silylated cyanohydrins in good yields (eq 3; Table 1). In the absence of tin catalyst under otherwise identical conditions, essentially no reaction is observed between Et_3SiCN and the illustrated substrates. Cyanosilylation proceeds smoothly both with aldehydes which are electronically deactivated toward addition (entries 5 and 6; 1,2-addition), as well as with those which are sterically hindered (entry 8). Although aliphatic ketones (e.g., 2-octanone) do not undergo appreciable reaction after days at room temperature,[9] Bu_3SnCN does effectively catalyze the cyanosilylation of 3,4-hexanedione (entry 9; single addition), an electronically activated ketone.



(3)



1

Figure 1. Proposed catalytic cycle for the Bu_3SnCN-catalyzed addition of R_3SiCN to aldehydes.

To date, efforts to develop a general, catalytic method for the enantioselective synthesis of cyanohydrins have focused largely on the use of chiral Lewis acids.[2] We have demonstrated that Bu_3SnCN serves as an efficient catalyst for cyanohydrin formation, by a mechanism presumably distinct from Lewis acid activation.[10] This observation opens the door to an approach to the catalytic asymmetric synthesis of cyanohydrins wherein the stereoselectivity is determined by the addition of a well-defined chiral tin cyanide to a carbonyl group, as opposed to the addition of an achiral cyanide to a carbonyl–(chiral Lewis acid) complex. Experiments directed toward demonstrating the viability of this strategy are underway.

Experimental Section

All substrates were obtained from Aldrich, with the exception of *trans*-2-hexenal and benzaldehyde, which were purchased from Alfa and Fisher, respectively; each substrate was purified by distillation immediately prior to use. Tributyltin cyanide (*toxic*!) was obtained from Aldrich and recrystallized from hexanes. Triethylsilyl cyanide (*toxic*!) was prepared according to the method of Becu and Anteunis.[11]

Analytical thin layer chromatography was accomplished using EM Reagents 0.25 mm silica gel 60 plates. Flash chromatography was performed on EM Reagents silica gel 60 (230–400 mesh).

^1H and ^{13}C nuclear magnetic resonance spectra were recorded on a Varian XL-300 NMR spectrometer at ambient temperature. ^1H data are reported as follows: chemical shift in parts per million downfield from tetramethylsilane (δ scale), multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet), integration, coupling constant (Hz), and assignment. ^{13}C chemical shifts are reported in ppm downfield from tetramethylsilane (δ scale). All ^{13}C spectra were determined with complete proton decoupling.

All reactions were carried out under an atmosphere of nitrogen in oven-dried glassware with magnetic stirring.

† Dedicated to Mary Fieser on the occasion of her 85th birthday.

(1) Pfizer Undergraduate Summer Research Fellow.

(2) For a recent review of asymmetric cyanohydrin synthesis, see: North, M. *Synlett* **1993**, 807–820.

(3) Herranz, R.; Castro-Pichel, J.; Garcia-Lopez, T. *Synthesis* **1989**, 703–706.

(4) For example, see: Ricci, A.; Roelens, S.; Vannucchi, A. *J. Chem. Soc., Chem. Commun.* **1985**, 1457–1458. See also: Evans, D. A.; Hoffman, J. M.; Truesdale, L. K. *J. Am. Chem. Soc.* **1973**, *95*, 5822–5823; Mai, K.; Patil, G. *J. Org. Chem.* **1986**, *51*, 3545–3548.

(5) *Chemistry of Pseudohalides*; Golub, A. M., Kohler, H., Skopenko, V. V., Ed.; Elsevier: New York, 1986.

(6) A number of catalysts for the addition of silyl cyanides to carbonyl groups have been reported. For early work, see: (a) ZnI_2, $AlCl_3$: Evans, D. A.; Truesdale, L. K.; Carroll, G. L. *J. Chem. Soc., Chem. Commun.* **1973**, 55–56. (b) KCN/18-crown-6: Evans, D. A.; Hoffman, J. M.; Truesdale, L. K. *J. Am. Chem. Soc.* **1973**, *95*, 5822–5823. Evans, D. A.; Truesdale, L. K. *Tetrahedron Lett.* **1973**, 4929–4932. (c) $AlCl_3$: Lidy, W.; Sundermeyer, W. *Chem. Ber.* **1973**, *106*, 587–593.

(7) For an outstanding overview, see: Rasmussen, J. K.; Heilmann, S. M.; Krepski, L. R. In *Advances in Silicon Chemistry*; Larson, G. L., Ed.; JAI Press: Greenwich, CT, 1991; pp 65–187.

(8) Bu_3SnCN also catalyzes the addition of Me_3SiCN and (*t*-Bu)-Me_2SiCN to aldehydes.

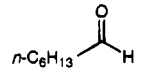
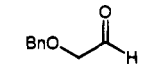
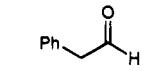
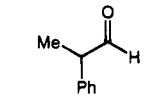
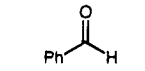
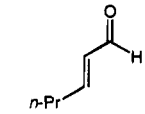
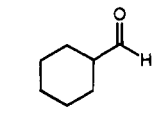
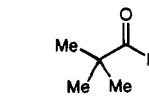
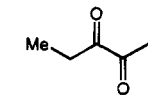
(9) Some catalysis by Bu_3SnCN is observed at elevated temperatures.

(10) We have shown that mixing equimolar quantities of Bu_3SnCN and pivalaldehyde affords the stannylated cyanohydrin quantitatively. Reaction of this species with Et_3SiCN produces the silylated cyanohydrin and regenerates Bu_3SnCN. More detailed mechanistic studies are in progress.

(11) Becu, C.; Anteunis, M. J. O. *Bull. Soc. Chim. Belg.* **1987**, *96*, 115–117.

0022-3263/94/1959-7178$04.50/0

Table 1. Bu_3SnCN-Catalyzed Cyanosilylation of Aldehydes and Activated Ketones (eq 3)

Entry	Substrate	Time (h)	Yield (%)
1		2	96
2		1	88
3		2	94
4		1	95 [a]
5		17	94
6		6 days	89
7		1	100
8		2	94
9		1	79

[a] 1.6 : 1 mixture of diastereomers.

Representative Procedure. Reaction of Heptanal with Triethylsilyl Cyanide Catalyzed by Tributyltin Cyanide. *n*-Heptanal (114 mg, 1.0 mmol) was added dropwise to a colorless solution of tributyltin cyanide (Aldrich; 31.6 mg, 0.10 mmol) in triethylsilyl cyanide (212 mg, 1.5 mmol) under nitrogen. The resulting homogeneous reaction mixture was stirred at room temperature for 2 h, at which time TLC showed the reaction to be complete. The mixture was purified directly by flash chromatography (5% EtOAc/hexanes), which afforded 247 mg (96%) of the silylated cyanohydrin. Notes: (1) The cyanosilylation proceeds smoothly, albeit more slowly, when run in a solvent (e.g., CH_2Cl_2 or benzene). (2) The cyanosilylation appears to proceed equally smoothly when run open to the atmosphere.

Each of the triethylsilyl (TES) cyanohydrins prepared according to this procedure was identical by ^1H and ^{13}C NMR spectroscopy with the product of the ZnI_2-catalyzed method of Evans.[6a]

Heptaldehyde, TES cyanohydrin: ^1H NMR (300 MHz, C_6D_6) δ 4.06 (t, 1H, J = 6.2, C*H*O), 1.55–1.05 (m, 10H, $(CH_2)_5CH_3$), 0.91 (t, 9H, J = 7.9, $Si(CH_2CH_3)_3$), 0.83 (t, 3H, J = 7.0, $CH_3(CH_2)_5$), 0.60–0.50 (m, 6H, $Si(CH_2CH_3)_3$); ^{13}C NMR (75 MHz, C_6D_6) δ 120.1, 61.9, 36.7, 31.8, 28.9, 24.7, 22.8, 14.1, 6.7, 4.6.

(Benzyloxy)acetaldehyde, TES cyanohydrin: ^1H NMR (300 MHz, C_6D_6) δ 7.15–7.00 (m, 5H, aromatic H), 4.20–4.10 (m, 3H, CH_2Ph, C*H*O), 3.28 (d, 2H, J = 5.5, CH_2CHO), 0.84 (t, 9H, J = 7.9, $Si(CH_2CH_3)_3$), 0.50–0.40 (m, 6H, $Si(CH_2CH_3)_3$); ^{13}C NMR (75 MHz, C_6D_6) δ 137.9, 128.6, 128.0, 127.8, 118.8, 73.6, 72.1, 62.0, 6.6, 4.6.

Phenylacetaldehyde, TES cyanohydrin: ^1H NMR (300 MHz, C_6D_6) δ 7.10–6.95 (m, 5H, aromatic H), 4.17 (t, 1H, J = 6.7, C*H*O), 2.72 (d, 2H, J = 6.7, CH_2Ph), 0.80 (t, 9H, J = 7.9, $Si(CH_2CH_3)_3$), 0.50–0.30 (m, 6H, $Si(CH_2CH_3)_3$); ^{13}C NMR (75 MHz, C_6D_6) δ 135.4, 130.0, 128.5, 127.4, 119.7, 63.1, 42.9, 6.5, 4.4.

2-Phenylpropionaldehyde, TES cyanohydrin: ^1H NMR (300 MHz, C_6D_6) **major isomer** δ 7.10–7.00 (m, 5H, aromatic H), 4.16 (d, 1H, J = 5.4, C*H*O), 2.85–2.75 (m, 1H, C*H*Ph), 1.27 (d, 3H, J = 6.9, CH_3CH), 0.84 (t, 9H, J = 8.1, $Si(CH_2CH_3)_3$), 0.50–0.35 (m, 6H, $Si(CH_2CH_3)_3$); **minor isomer** δ 7.10–7.00 (m, 5H, aromatic H), 4.12 (d, 1H, J = 6.8, C*H*O), 2.85–2.75 (m, 1H, PhC*H*), 1.26 (d, 3H, J = 6.9, CH_3CH), 0.83 (t, 9H, J = 7.9, $Si(CH_2CH_3)_3$), 0.50–0.35 (m, 6H, $Si(CH_2CH_3)_3$); ^{13}C NMR (75 MHz, C_6D_6) δ 140.8, 140.8, 128.7, 128.5, 128.4, 128.3, 127.6, 119.4, 119.1, 67.9, 67.1, 45.6, 45.2, 15.7, 15.2, 6.6, 4.5, 4.5.

Benzaldehyde, TES cyanohydrin: ^1H NMR (300 MHz, C_6D_6) δ 7.35–7.00 (m, 5H, aromatic H), 5.13 (s, 1H, C*H*O), 0.87 (t, 9H, J = 7.9, $Si(CH_2CH_3)_3$), 0.55–0.45 (m, 6H, $Si(CH_2CH_3)_3$); ^{13}C NMR (75 MHz, C_6D_6) δ 137.2, 129.2, 129.0, 126.5, 119.4, 64.0, 6.6, 4.6.

***trans*-2-Hexenal, TES cyanohydrin**: ^1H NMR (300 MHz, C_6D_6) δ 5.69 (ddt, 1H, J = 15.1, 1.2, 6.9, C*H*CH_2), 5.32 (ddt, 1H, J = 15.1, 6.1, 2.8, C*H*CHO), 4.52 (dd, 1H, J = 6.1, 1.4, C*H*O), 1.70 (app. q, 2H, J = 7.2, CH_2CH), 1.13 (app. sextet, 2H, J = 7.4, CH_2CH_2CH), 0.92 (t, 9H, J = 7.9, $Si(CH_2CH_3)_3$), 0.72 (t, 3H, J = 7.3, $CH_3(CH_2)_2$), 0.60–0.50 (m, 6H, $Si(CH_2CH_3)_3$); ^{13}C NMR (75 MHz, C_6D_6) δ 135.4, 126.0, 118.9, 62.5, 33.9, 21.9, 13.6, 6.6, 4.7.

Cyclohexanecarboxaldehyde, TES cyanohydrin: ^1H NMR (300 MHz, C_6D_6) δ 3.90 (d, 1H, J = 5.7, C*H*O), 1.80–0.95 (m, 11H, ring H), 0.92 (t, 9H, J = 7.8, $Si(CH_2CH_3)_3$), 0.60–0.50 (m, 6H, $Si(CH_2CH_3)_3$); ^{13}C NMR (75 MHz, C_6D_6) δ 119.4, 66.8, 43.4, 28.1, 26.2, 25.8, 6.7, 4.6.

Trimethylacetaldehyde, TES cyanohydrin: ^1H NMR (300 MHz, C_6D_6) δ 3.74 (s, 1H, C*H*O), 0.92 (t, 9H, J = 7.8, $Si(CH_2CH_3)_3$), 0.88 (s, 9H, $(CH_3)_3C$), 0.60–0.50 (m, 6H, $Si(CH_2CH_3)_3$); ^{13}C NMR (75 MHz, C_6D_6) δ 119.1, 71.1, 36.0, 24.9, 6.7, 4.6.

3,4-Hexanedione, TES cyanohydrin: ^1H NMR (300 MHz, C_6D_6) δ 2.26 (q, 2H, J = 7.4, $CH_3CH_2C{=}O$), 1.65–1.45 (m, 2H, CH_3CH_2CCN), 0.94 (t, 9H, J = 7.7, $Si(CH_2CH_3)_3$), 0.86 (t, 3H, J = 7.1, CH_3CH_2CN), 0.79 (t, 3H, J = 7.5, $CH_3CH_2CC{=}O$), 0.75–0.65 (m, 6H, $Si(CH_2CH_3)_3$); ^{13}C NMR (75 MHz, C_6D_6) δ 203.9, 118.8, 79.2, 33.2, 29.9, 7.9, 7.6, 6.9, 5.8.

Acknowledgment. Support has been provided by the Camille and Henry Dreyfus Foundation (New Faculty Award in Chemistry), the National Science Foundation, the MIT Undergraduate Research Opportunities Program, and the Pfizer Undergraduate Summer Research Fellowship Program. Acknowledgement is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research.