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Convenient and Efficient Conversion of Aldehydes to Acylated Cyanohydrins Using Tributyltin Cyanide as a Catalyst[†]

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Acylated cyanohydrins are important synthetic targets due to their application industrially as pesticides[2] and their utility as precursors to many useful classes of organic compounds.[3,4] As part of a research program in organotin chemistry which is focused on the design of new catalytic processes,[5] we report herein a convenient, mild, and efficient method for generating acylated cyanohydrins from aldehydes.[6]

Our new catalytic process for converting aldehydes to acylated cyanohydrins employs Bu_3SnCN as the catalyst and acetyl cyanide or methyl cyanoformate as the stoichiometric addend (Figure 1; Y = Me or OMe, respectively). The design of this catalytic cycle was based on two separate observations reported by others, namely, that Bu_3SnCN will add to an aldehyde[7] and that Bu_3Sn(O-*i*-Pr) will react with acetyl cyanide to afford Bu_3SnCN.[8] We anticipated that these two transformations, proceeding in sequence, would constitute a new catalytic process, the tin cyanide-catalyzed addition of acyl cyanides to aldehydes (Figure 1).

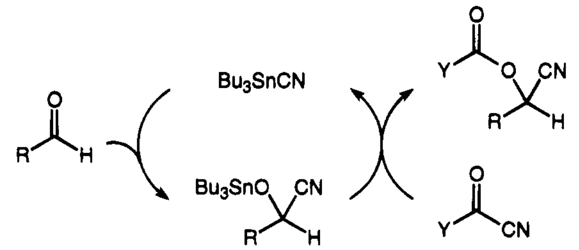
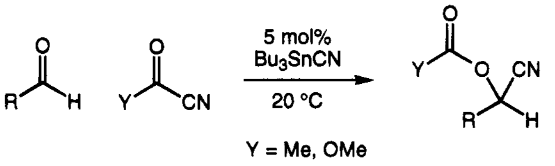
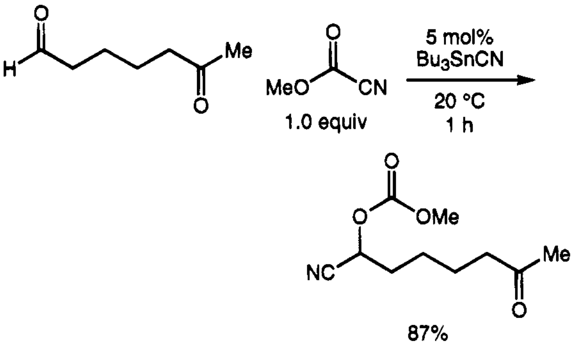


Figure 1. Catalytic cycle for the Bu_3SnCN-catalyzed addition of acyl cyanides to aldehydes.

We have now shown that the proposed catalytic cycle is in fact viable. Thus, treatment of an aldehyde with 5 mol % Bu_3SnCN and 1.2−1.5 equiv of either acetyl cyanide or methyl cyanoformate neat at room temperature provides the acylated cyanohydrin in good to excellent yields (eq 1; Table 1).[9] A wide array of aldehydes cleanly undergo reaction, including those in which the carbonyl group is electronically deactivated toward addition (entries 6[10] and 7) or sterically hindered (entry 8). No reaction occurs between an aldehyde and either acyl cyanide in the absence of Bu_3SnCN. Because ketones do not undergo addition under the standard catalytic conditions, the selective cyanoacylation of a ketoaldehyde can be achieved (eq 2).



(1)



(2)

From the standpoints of yield and experimental simplicity, this Bu_3SnCN-catalyzed process represents an attractive alternative to earlier methods[6] for synthesizing acylated cyanohydrins.

Experimental Section

General. 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. Methyl cyanoformate and pyruvonitrile were purchased from Aldrich and purified by distillation.

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).

All ^{1}H NMR *J* values are given in Hz.

Microanalyses were performed by E + R Microanalytical Laboratory, Inc.

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

Representative Procedure. Reaction of Heptanal with Methyl Cyanoformate Catalyzed by Tributyltin Cyanide. *n*-Heptanal (114 mg, 1.0 mmol) was added to a colorless solution of tributyltin cyanide (15.8 mg, 0.05 mmol) in methyl cyanoformate (106 mg, 1.25 mmol). The resulting homogeneous reaction mixture was stirred at room temperature for 1 h, at which time

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[†] Dedicated to Professor Frederick D. Greene on the occasion of his retirement.

[1] Pfizer Undergraduate Summer Research Fellow.

[2] (a) *Agrochemicals from Natural Products*; Godfrey, C. R. A., Ed.; Marcel Dekker: New York, 1995. (b) *Synthetic Pyrethroids*; Elliott, M., Ed.; ACS Symposium Series 42; American Chemical Society: Washington, DC, 1977.

[3] For a recent review of the synthesis and reactions of cyanohydrins, see: Effenberger, F. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1555−1564.

[4] For example, see: (a) Lu, Y.; Miet, C.; Kunesch, N.; Poisson, J. E. *Tetrahedron: Asymmetry* **1993**, *4*, 893−902. (b) Abe, H.; Nitta, H.; Mori, A.; Inoue, S. *Chem. Lett.* **1992**, 2443−2446. (c) Inagaki, M.; Hiratake, J.; Nishioka, T.; Oda, J. *J. Am. Chem. Soc.* **1991**, *113*, 9360−9361. (d) Matsuda, F.; Matsumoto, T.; Ohsaki, M.; Ito, Y.; Terashima, S. *Chem. Lett.* **1990**, 723−724. (e) Babler, J. H.; Marcuccilli, C. J.; Oblong, J. E. *Synth. Commun.* **1990**, *20*, 1831−1836. (f) Ohta, H.; Kimura, Y.; Sugano, Y.; Sugai, T. *Tetrahedron* **1989**, *45*, 5469−5476. (g) Wang, Y.-F.; Chen, S.-T.; Liu, K. K.-C.; Wong, C.-H. *Tetrahedron Lett.* **1989**, *30*, 1917−1920. (h) Matsuo, N.; Ohno, N. *Tetrahedron Lett.* **1985**, *26*, 5533−5534. (i) Au, A. T. *Synth. Commun.* **1984**, *14*, 749−753. (j) Uff, B. C.; Al-Kolla, A.; Adamali, K. E.; Harutunian, V. *Synth. Commun.* **1978**, *8*, 163−167.

[5] Scholl, M.; Fu, G. C. *J. Org. Chem.* **1994**, *59*, 7178−7179.

[6] For examples of other approaches, see: (a) Francis, F.; Davis, O. C. M. *J. Chem. Soc.* **1909**, *95*, 1403−1411. (b) McIntosh, J. M. *Can. J. Chem.* **1977**, *55*, 4200−4205. (c) Au, A. T. *Synth. Commun.* **1984**, *14*, 743−748. (d) Ohta, H.; Kimura, Y.; Sugano, Y.; Sugai, T. *Tetrahedron* **1989**, *45*, 5469−5476. (e) Hoffmann, H. M. R.; Ismail, Z. M.; Hollweg, R.; Zein, A. R. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 1807−1810 and references cited therein.

[7] Herranz, R.; Castro-Pichel, J.; Garcia-Lopez, T. *Synthesis* **1989**, 703−706.

[8] Gorsi, B. L.; Mehrotra, R. C. *Indian J. Chem., Sect. A* **1977**, *15*, 1099−1101.

[9] The addition of pyruvonitrile to *trans*-3-hexenal or benzaldehyde requires more vigorous conditions (10 mol % Bu_3SnCN, ~5 equiv of pyruvonitrile, 50 °C).

[10] 1,2-Addition is observed.

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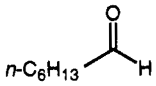
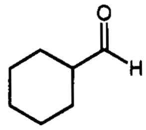
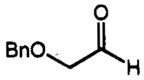
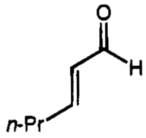
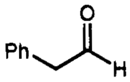
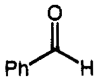
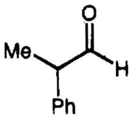
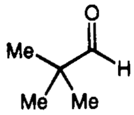
Table 1. Bu_3SnCN-Catalyzed Cyanoacylation of Aldehydes and Activated Ketones (eq 1)

Entry	Substrate	Time (h)	Yield (%) Top: Y = OMe Bottom: Y = Me	Entry	Substrate	Time (h)	Yield (%) Top: Y = OMe Bottom: Y = Me
1		1 4	92 98	5		1 5	97 96
2		1 4	91 94	6		6 days 30	82 78
3		36 5	94 90	7		36 10	92 89
4		2 4	95[a] 98[a]	8		14 5	94 83

[a] ~1.5:1 mixture of diastereomers.

TLC showed the reaction to be complete. The product was purified directly by flash chromatography (25% EtOAc/hexanes), which afforded 183 mg (92%) of the acylated cyanohydrin, a colorless oil. *Note:* (1) The reaction does not appear to be oxygen- or moisture-sensitive—when it is run in air, a comparable yield of product is observed. (2) The procedure for the catalyzed addition of pyruvonitrile to aldehydes is identical to that described for methyl cyanoformate, except that 1.5 equiv of pyruvonitrile are used.

Heptaldehyde, methyl cyanoformate adduct: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.17 (t, 1H, J = 6.6), 3.84 (s, 3H), 1.94 (app q, 2H, J = 6.6), 1.55–1.20 (m, 8H), 0.87 (t, 3H, J = 6.7); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.2, 116.4, 64.9, 55.6, 32.2, 31.3, 28.3, 24.2, 22.3, 13.8; IR (neat) 2958, 2932, 2860, 1762, 1444, 1264, 976, 938, 789 cm^{-1}: HRMS calcd for $C_{10}H_{17}NO_3$ 199.1208, found 199.1203. Anal. Calcd for $C_{10}H_{17}NO_3$: C, 60.28; H, 8.60. Found: C, 60.46; H, 8.66.

(Benzyloxy)acetaldehyde, methyl cyanoformate adduct: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40–7.30 (m, 5H), 5.36 (t, 1H, J = 5.5), 4.62 (s, 2H), 3.85 (s, 3H), 3.80 (d, 2H, J = 5.4); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.9, 136.5, 128.5, 128.1, 127.7, 114.7, 73.6, 67.9, 64.0, 55.8; IR (neat) 2959, 1766, 1443, 1268, 1116, 1028, 941, 787, 741, 700 cm^{-1}; HRMS calcd for $C_{12}H_{13}NO_4$ 235.0845, found 235.0842.

Phenylacetaldehyde, methyl cyanoformate adduct: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35–7.20 (m, 5H), 5.33 (t, 1H, J = 7.2), 3.82 (s, 3H), 3.21 (d, 2H, J = 7.0); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.0, 132.9, 129.5, 128.8, 127.9, 116.0, 65.5, 55.7, 38.5; IR (neat) 2960, 1762, 1443, 1260, 1000, 932, 753, 700, 541 cm^{-1}; HRMS calcd for $C_{11}H_{11}NO_3$ 205.0739, found 205.0736.

2-Phenylpropionaldehyde, methyl cyanoformate adduct: ^{1}H NMR (300 MHz, $CDCl_3$) **major isomer** δ 7.40–7.20 (m, 5H), 5.25 (d, 1H, J = 6.9), 3.82 (s, 3H), 3.33 (app pentet, 1H, J = 7.0), 1.48 (d, 3H, J = 7.0); **minor isomer** δ 7.40–7.20 (m, 5H), 5.29 (d, 1H, J = 7.0), 3.79 (s, 3H), 3.33 (app pentet, 1H, J = 7.0), 1.52 (d, 3H, J = 7.5); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.2, 154.0, 138.5, 138.3, 128.8, 128.1, 127.9, 127.9, 127.8, 127.7, 115.6, 115.3, 69.8, 69.3, 55.7, 55.7, 42.1, 41.8, 16.1, 15.6; IR (neat) 2964, 1762, 1447, 1345, 1266, 1112, 981, 786, 767, 702 cm^{-1}; HRMS calcd for $C_{12}H_{13}NO_3$ 219.0895, found 219.0892.

Cyclohexanecarboxaldehyde, methyl cyanoformate adduct: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.02 (d, 1H, J = 5.8), 3.84 (s, 3H), 1.90–1.10 (m, 11H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.3, 115.7, 69.4, 55.6, 40.0, 27.8, 27.6, 25.6, 25.2, 25.1; IR (neat) 2933, 2857, 1770, 1444, 1348, 1318, 1289, 983, 789 cm^{-1}; HRMS calcd for $C_{10}H_{15}NO_3$ 197.1052, found 197.1050.

***trans*-2-Hexenal, methyl cyanoformate adduct:** ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.16 (dt, 1H, J = 14.6, 7.1), 5.65 (d, 1H, J = 7.0), 5.56 (dd, 1H, J = 15.3, 8.9), 3.84 (s, 3H), 2.10 (app q, 2H, J = 7.6), 1.44 (app sex, 2H, J = 7.4), 0.90 (t, 3H, J = 7.3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.9, 141.2, 119.6, 115.2, 65.1, 55.5, 33.9, 21.3, 13.4; IR (neat) 2962, 2934, 2875, 1759, 1443, 1256, 1107, 966, 787 cm^{-1}; HRMS calcd for $C_9H_{13}NO_3$ 183.0895, found 183.0894.

Benzaldehyde, methyl cyanoformate adduct: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55–7.40 (m, 5H), 6.25 (s, 1H), 3.85 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.9, 131.1, 130.5, 129.2, 127.8, 115.6, 66.5, 55.8; IR (neat) 2960, 1754, 1456, 1443, 1318, 1256, 1194, 994, 950, 796, 766, 696 cm^{-1}; HRMS calcd for $C_{10}H_9NO_3$ 191.0582, found 191.0583.

Trimethylacetaldehyde, methyl cyanoformate adduct: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.86 (s, 1H), 3.81 (s, 3H), 1.06 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.4, 115.5, 73.3, 55.6, 34.8, 24.9; IR (neat) 2969, 1762, 1444, 1372, 1306, 1266, 982, 936 cm^{-1}; HRMS calcd for $C_8H_{13}NO_3$ 171.0895, found 171.0893. Anal. Calcd for $C_8H_{13}NO_3$: C, 56.13; H, 7.65. Found: C, 56.27; H, 7.73.

6-Oxoheptanal, methyl cyanoformate mono-adduct (eq 2): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.15 (t, 1H, J = 6.6), 3.81 (s, 3H), 2.43 (t, 2H, J = 7.0), 2.09 (s, 3H), 1.90 (app q, 2H, J = 7.3), 1.60–1.40 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.9, 154.1, 116.2, 64.6, 55.7, 42.9, 32.1, 29.8, 23.9, 22.6; IR (neat) 2959, 1758, 1715, 1443, 1356, 1264, 1162, 936, 789 cm^{-1}; HRMS calcd for $C_{10}H_{15}NO_4$ 213.1001, found 213.0996.

Heptaldehyde, pyruvonitrile adduct: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.29 (t, 1H, J = 6.8), 2.12 (s, 3H), 1.88 (app q, 2H, J = 7.5), 1.55–1.20 (m, 8H), 0.87 (t, 3H, J = 6.7); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.2, 116.9, 61.1, 32.2, 31.4, 28.4, 24.4, 22.4, 20.4, 13.9; IR (neat) 2931, 2860, 1755, 1467, 1373, 1219, 1121, 1037, 914, 726 cm^{-1}. Anal. Calcd for $C_{10}H_{17}NO_2$: C, 65.54; H, 9.35. Found: C, 65.36; H, 9.27.

(Benzyloxy)acetaldehyde, pyruvonitrile adduct: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40–7.25 (m, 5H), 5.48 (t, 1H, J = 5.8), 4.62 (d, 2H, J = 2.9), 3.77 (d, 3H, J = 5.3), 2.14 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.8, 136.6, 128.5, 128.1, 127.7, 115.2, 73.6, 68.0, 60.3, 20.2; IR (neat) 2871, 1754, 1454, 1372, 1218, 1124, 1046, 743, 700 cm^{-1}; HRMS calcd for $C_{12}H_{13}NO_3$ 219.0895, found 219.0898.

Phenylacetaldehyde, pyruvonitrile adduct: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40–7.20 (m, 5H), 5.46 (t, 1H, J = 7.1), 3.17 (d, 2H, J = 7.1), 2.10 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.9, 133.2, 129.5, 128.8, 127.8, 116.4, 61.8, 38.5, 20.2; IR (neat) 3032, 1755, 1497, 1456, 1373, 1224, 1084, 1036, 753, 701 cm^{-1}; HRMS calcd for $C_{11}H_{11}NO_2$ 189.0789, found 189.0788.

2-Phenylpropionaldehyde, pyruvonitrile adduct: ^{1}H NMR (300 MHz, $CDCl_3$) **major isomer** δ 7.40–7.20 (m, 5H), 5.41 (d, 1H, J = 5.9), 3.28 (m, 1H), 2.11 (s, 3H), 1.45 (d, 3H, J = 7.5); **minor isomer** δ 7.40–7.20 (m, 5H), 5.43 (d, 1H, J = 7.0), 3.28 (m, 1H), 2.04 (s, 3H), 1.51 (d, 3H, J = 6.4); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.9, 168.8, 138.8, 138.7, 128.7, 127.9, 127.8, 127.6, 115.9, 115.8, 66.0, 65.5, 41.8, 41.8, 20.2, 20.2, 16.2, 15.7;

IR (neat) 2977, 1754, 1496, 1454, 1373, 1219, 1039, 763, 702 cm^{-1}; HRMS calcd for $C_{12}H_{13}NO_2$ 203.0946, found 203.0948.

Cyclohexanecarboxaldehyde, pyruvonitrile adduct: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.16 (d, 1H, J = 6.0), 2.12 (s, 3H), 1.95–1.05 (m, 11H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.2, 116.1, 65.5, 39.9, 28.0, 27.8, 25.7, 25.3, 25.2, 20.3; IR (neat) 2933, 2857, 1755, 1452, 1372, 1221, 1030 cm^{-1}; HRMS calcd for $C_{10}H_{15}NO_2$ 181.1102, found 181.1101.

***trans*-2-Hexenal, pyruvonitrile adduct:** This reaction was run with 10 mol % Bu_3SnCN and 5.0 equiv of pyruvonitrile at 45 °C: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.12 (dt, 1H, J = 15.0, 7.1), 5.78 (d, 1H, J = 6.9), 5.52 (dd, 1H, J = 15.4, 6.6), 2.12 (s, 3H), 2.09 (app q, 2H, J = 7.7), 1.43 (app sex, 2H, J = 7.4), 0.90 (t, 3H, J = 7.3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.8, 140.3, 120.1, 115.7, 61.4, 33.9, 21.4, 20.3, 13.4; IR (neat) 2962, 2934, 1754, 1372, 1218, 1023, 969 cm^{-1}; HRMS calcd for $C_9H_{13}NO_2$ 167.0946, found 167.0948.

Benzaldehyde, pyruvonitrile adduct: This reaction was run with 10 mol % Bu_3SnCN and 4.5 equiv of pyruvonitrile at 50 °C: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55–7.40 (m, 5H), 6.40 (s, 1H), 2.15 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.8, 131.7, 130.3, 129.1, 127.8, 116.0, 62.7, 20.3; IR (neat) 3038, 2944, 1756, 1496, 1457, 1372, 1211, 1024, 1002, 962, 899, 759, 697 cm^{-1}; HRMS calcd for $C_{10}H_9NO_2$ 175.0633, found 175.0633.

Trimethylacetaldehyde, pyruvonitrile adduct: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.05 (s, 1H), 2.15 (s, 3H), 1.07 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.2, 116.0, 69.3, 34.5, 25.1, 20.2; IR (neat) 2971, 1755, 1481, 1468, 1373, 1232, 1219, 1055, 1026, 903 cm^{-1}. Anal. Calcd for $C_8H_{13}NO_2$: C, 61.91; H, 8.44. Found: C, 62.13; H, 8.58.

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Supporting Information Available: ^{1}H NMR spectra for all reaction products (17 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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