Tributyltin Cyanide-Catalyzed Addition of Methyl Cyanoformate to Aldehydes at the Organic Solvent

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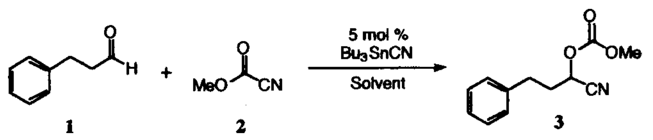
Formylated cyanohydrins are important synthetic targets due to their application industrially as pesticides[1] and their utility as precursors to many useful classes of organic compounds.[2] Recently, Fu and his coworkers reported that tributyl tin cyanide as an efficient catalysts for the acylated cyanohydrin of aldehydes without solvent.[3] The organic reaction is important to carry out in the solvent system. The solvent[4] can effect the reaction rate and control the concentration of reaction mixture. 1) We investigated the convinient and efficient method for generating formylated cyanohydrins in the organic solvent systems which are dichloromethane (CH_2Cl_2), THF, diethyl ether, acetonitrile (CH_3CN), and DMF as polar aprotic solvent. 2) We investigated the temperature effect in this reaction, also. Treatment of hydrocinamaldehyde **1** and methyl cyanoformate **2** with tributyltin cyanide in various organic solvents at room temperature to afford the expected *O*-methoxycarbonyl cyanohydrin **3** (Scheme 1). In this study, we found that acetonitrile (CH_3CN) is moderate solvent in this cyanohydrin formylation.

The other results of the cyanohydrin formylation in different solvents are shown in Table 1. The reaction does not work in THF, dichoromethane (CH_2Cl_2), or diethylether, but the reaction was proceeded slightly in DMF and acetonitrile (CH_3CN) for 2 hrs at room temperature in 25-30% yields.

We tried to improve the yield using the different temperatures and pressure. Hydrocinnamaldehyde **1** react with methyl cyanoformate **2** in the presence of catalytic amount of tributyltin cyanide in acetonitrile for 2 hrs in sealed tube at 80 °C, to give the corresponding *O*-methoxycarbonyl cyanohydrine **3** in 79% yield. Treatment of various aldehydes with 5 mol% Bu_3SnCN and 1.25 equiv of methylcyanoformate in acetonitrile at 80 °C in the sealed tube provides the O-methoxycarbonyl cyanohydrine derivatives in good yields (Table 2).

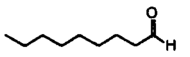
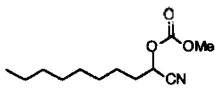
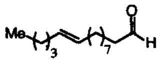
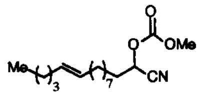
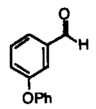
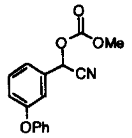
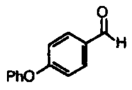
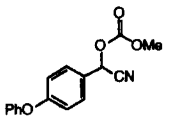
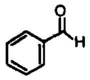
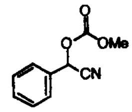


Scheme 1.

Table 1. Bu_3SnCN-catalyzed cyanoformylatin of hydrcinnamaldehyde in various solvent at room temperature

Entry	Solvent	Time	Yield
1	THF	2.0 hr	no rxn
2	CH_2Cl_2	2.0 hr	no rxn
3	ethylether	2.0 hr	no rxn
4	CH_3CN	2.0 hr	25%
5	DMF	2.0 hr	30%

Table 2. Bu_3SnCN-catalyzed cyanoformylation of aldehyde in CH_3CN

Aldehydes	Cyanohydrin	Time (hr)	Yield (%)
 4	 5	2.5	81
 6	 7	2.5	80
 8	 9	2.0	78
 10	 11	3.0	69
 12	 13	2.5	78

In summary, we have developed a simple procedure for converting aldehydes to formylated cyanohydrins with methyl cyanoformate using tributyltin cyanide as a catalyst in acetonitrile at 80 °C. Efforts directed toward the development of organotin reagents for stereoselective synthesis of formylated cyanohydrin derivatives are in progress.

Experimental

General. Nuclear magnetic resonance (^1H and ^{13}C NMR) spectra were recorded on Varian Gemini 2000 (300 MHz) spectrometers. Chemical shifts are reported in parts per million (δ) downfield from tetramethylsilane. Coupling constants (J values) are given in hertz (Hz), and spin multiplicities are indicated by the following symbols: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). Deuterated NMR solvents contained 99.0-99.8% deuterium in the indicated position.

Infrared spectra were recorded on a Nicolet Impact 410 FT-IR spectrophotometer. Band positions are given in reciprocal centimeters (cm^{-1}) and relative intensities are listed as: br (broad), s (strong), m (medium), or w (weak).

Thin layer chromatography (tlc) was performed on 0.25 mm Merck silica-coated glass plates, with the compounds being identified in one or more of the following manners: UV (254 nm, unless otherwise specified), iodine. Flash chromatography was performed according to the procedure of Still[5] using thick-walled glass columns and Merck Silica Gel 60 (230-400 Mesh). All solvents were distilled from calcium chloride before use unless noted otherwise. Tetrahydrofuran (THF), diethyl ether (Et_2O), and hexanes were distilled from sodium/benzophenone ketyl. All reagents were distilled, recrystallized, or chromatographed prior to use unless otherwise noted.

Glassware used in the reactions described below was dried in an oven at 120 °C overnight (12 hours) and assembled under an inert atmosphere of nitrogen, or flame-dried under vacuum and then cooled under nitrogen.

***O*-Methoxycarbonyl cyanohydrin 3.** The solution of tributyltin cyanide (22 mg, 0.07 mol) in dried acetonitrile (5 mL) was added methyl cyanoformate (160 mg, 1.86 mmol) and hydrocynnamaldehyde (200 mg, 1.49 mmol) in sealed tube at room temperature. The reaction mixture was stirred at 80 °C for 2.5 h. The reaction mixture was extracted with EtOAc (3×50 ml) after evaporated acetonitrile in the rotavapor. The organic layer was dried (Na_2SO_4), and concentrated in *vacuo* to give crude solid. Purification by flash chromatography (25% EtOAc/hexane) afforded 239 mg (79%) of methyl cyanoformate **3**. Rf 0.67, 25% EtOAc/hexane; IR (neat) 3060 (m), 2960 (s), 2930 (m), 2890 (m), 2210 (w), 1760 (s), 1700 (s), 1490 (s); ^{1}H NMR ($CDCl_3$): 2.34-2.23 (m, 2H), 2.86 (t, 2H, *J*=7.7), 3.88 (s, 3H), 5.15 (t, 1H, *J*=6.8), 7.34-7.18 (m, 5H).

Formylated cyanohydrin 5. IR (neat) 2940 (s), 2920 (s), 2840 (s), 2190 (w), 1760 (s), 1440 (s); ^{1}H NMR ($CDCl_3$): 0.86 (t, 3H, *J*=6.41), 1.25-1.53 (m, 12H), 1.86-1.94 (m, 2H), 3.83 (s, 3H), 5.17 (t, 1H, *J*=6.72).

Formylated cyanohydrin 7. IR (neat) 3000 (m), 2930 (s), 2860 (s), 2300 (w), 1760 (s), 1430 (s), 1270 (s); ^{1}H NMR ($CDCl_3$): 0.90 (t, 3H, *J*=6.59), 1.29-1.60 (m, 18H), 1.89-2.03 (m, 6H), 3.86 (s, 3H), 5.20 (t, 1H, *J*=6.74), 5.32-5.37 (m, 2H).

Formylated cyanohydrin 9. IR (neat) 3040 (m), 3020 (m), 2940 (w), 2840 (w), 2270 (w), 1770 (s), 1580 (s); ^{1}H NMR ($CDCl_3$): 3.88 (s, 3H), 6.23 (s, 1H), 7.02-7.42 (m, 9H).

Formylated cyanohydrin 11. IR (neat) 3060 (m), 3030 (s), 2990 (m), 2940 (s), 2960 (w), 2270 (w), 1760 (s), 1560 (s); ^{1}H NMR ($CDCl_3$): 3.88 (s, 3H), 6.24 (s, 1H), 7.01-7.52 (m, 9H).

Formylated cyanohydrin 13. IR (neat) 3040 (m), 3010 (m), 3000 (m), 2960 (s), 2200 (w), 1770 (s), 1500 (m), 1410 (s); ^{1}H NMR ($CDCl_3$): 3.85 (s, 3H), 6.25 (s, 1H), 7.40-7.55 (m, 5H).

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Ozonolyses of Vinyl Triflates

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Olefins which bear electronegative substituents in a vinylic position such as **1a**[1], **1b**[2] or **1c**[3] are preferentially cleaved by ozone to give fragments of types **2** and **3**. Due to the low dipolarophilicity of acid derivatives such as **3a**-**3c**, cycloadditions of fragments of types **2** and **3** to give ozonides of type **4** are disfavored. Hence, it is not surprising that ozonolyses of substrates of types **1a**[4], **1b**[2] and **1c**[5,6] afford the corresponding ozonides in low yield or not at all, depending on the nature of the substituents at the double bonds of **1a**-**1c**. In the present work we were interested in the behavior of vinyl triflates towards ozone since, to our knowledge, such reactions have not been reported. Since it was apparent from previous work,[7] that ozonlysis of olefinic substrates on polyethylene is a more suitable technique than ozonolysis in solution, the ozonolyses of **5** and **14** were carried out on polyethylene.