A New Synthesis of Allenic Nitriles from Ynones *via* Cyano Phosphates

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Ynone cyanohydrin diethyl phosphates (cyano phosphates) 2 reacted regioselectively with higher-order cuprates 3, generated from 2-thienyl(cyano)copper lithium and *n*-butyl lithium, to give trisubstituted allenic nitriles 4 through an *S*N2′ process in good yields. On the other hand, reaction of an excess of dialkyl copper lithium with ynone cyano phosphates 2 afforded allylic nitriles 5, *via* allenic nitriles 4.

Keywords ynone; ynal; diethyl phosphorocyanidate; lithium cyanide; cyano phosphate; higher-order cuprate; allenic nitrile; allylic nitrile; *S*N2′ process

Allenic nitriles are useful intermediates for the synthesis of heteroaromatic compounds.[1] Two general methods for the synthesis of allenic nitriles have so far been reported: i) treatment of propargyl alcohols with copper(I)cyanide (CuCN), a trace of copper, potassium cyanide, and 48% hydrobromic acid,[1] ii) treatment of bromoallenes with CuCN in dimethylformamide.[2] These methods, however, usually require a long reaction time and high reaction temperature. Moreover, little is known about the preparation of trisubstituted allenic nitriles. We have already demonstrated that cyanohydrin *O,O′*-diethyl phosphates (cyano phosphates), which can be readily obtained from various kinds of ketones and aldehydes by reaction with diethyl phosphorocyanidate (DEPC) and lithium cyanide (LiCN), serve as versatile intermediates in organic synthesis.[3] Our recent work also showed that cyano phosphates of α,β-unsaturated carbonyl compounds react with organocopper reagents[4] to give γ-alkylated α,β-unsaturated nitriles *via* an *S*N2′ process.[5]

In a continuation of our work on the synthetic utility of the cyano phosphates, this paper presents an efficient method for the synthesis of trisubstituted allenic nitriles **4** from ynone cyano phosphates **2** by regioselective alkylation with organocopper reagents **3**.

Results and Discussion

Treatment of the ynone **1a** with DEPC (3 eq) and LiCN (3 eq) in tetrahydrofuran (THF) instantly afforded the cyano phosphate **2a** (R^1 = Bu, R^2 = Me), which was, without purification, allowed to react with lithium dibutylcuprate (n-Bu_2CuLi) **3a** (1.4 eq) to give the allenic nitrile **4a** in 66% yield. The structural assignment was achieved by examination of the infrared (IR) [2220 (CN) and 1950 cm^{-1} (C=C=C)] and carbon-13 nuclear magnetic resonance (^{13}C-NMR) (δ 215 ppm, C=$\underline{C}$=C) spectra. Examination of the proton nuclear magnetic resonance (^{1}H-NMR) spectrum of the crude product did not reveal any substitution of the cuprate for the diethyl phosphonooxy group. When the so-called higher-order cuprate [n-Bu(2-Th)Cu(CN)Li_2]**3b**,[6] generated *in situ* from 2-thienyl(cyano)copper lithium [(2-Tu)Cu(CN)Li] (1.4 eq) and *n*-BuLi, was used as an alkylating agent, the yield of **4a** was improved to 87%. Thus, the scope and limitation of the allenic nitrile synthesis were examined by using some higher-order cuprates, as illustrated in Table I.

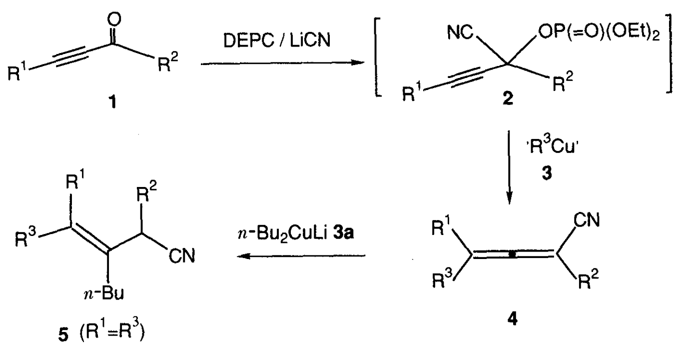
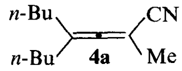
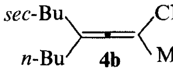
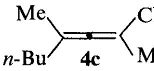
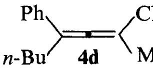
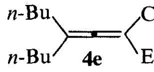
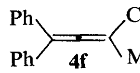
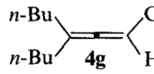


Chart 1

The aliphatic ynones **1a** and **1b** readily reacted with alkyl higher-order cuprates **3b**—**3d** as well as the aryl higher-order cuprate **3e** to give allenic nitriles **4a**—**4e** *via* cyano phosphates **2** in good yields. The aromatic ynone **1c** was also alkylated with alkyl or aryl higher-order cuprates **3b** (or **3e**) to give allenic nitriles **4d** (or **4f**) regioselectively. On the other hand, the conversion of the ynal **1d** to the corresponding allenic nitrile **4g** *via* **2** proceeded in only

Table I. Synthesis of Allenic Nitriles from Ynones and an Ynal *via* Cyano Phosphates

Ynone or ynal Compd. No.	Cuprate No.	Product No.	Yield (%)[a]
n-Bu—≡—COMe **1a**	n-Bu_2CuLi **3a**	 *n*-Bu, *n*-Bu, CN, Me **4a**	66
1a	n-Bu(2-Th)Cu(CN)Li_2 **3b**	**4a**	87
1a	*sec*-Bu(2-Th)Cu(CN)Li_2 **3c**	 *sec*-Bu, *n*-Bu, CN, Me **4b**	63
1a	Me(2-Th)Cu(CN)Li_2 **3d**	 Me, *n*-Bu, CN, Me **4c**	75
1a	Ph(2-Th)Cu(CN)Li_2 **3e**	 Ph, *n*-Bu, CN, Me **4d**	72
n-Bu—≡—COEt **1b**	**3b**	 *n*-Bu, *n*-Bu, CN, Et **4e**	66
Ph—≡—COMe **1c**	**3b**	**4d**	69
1c	**3e**	 Ph, Ph, CN, Me **4f**	53
n-Bu—≡—CHO **1d**	**3b**	 *n*-Bu, *n*-Bu, CN, H **4g**	32

a) Isolated yield.

32% yield, because of the instability of the ynal cyano phosphate **2**.

Furthermore, it was found that the ynone cyano phosphates **2a** reacted with an excess of n-Bu$_2$CuLi **3a** (3 eq) to give the allylic nitrile **5a** ($R^1 = R^3 = R^4 = n$-Bu, $R^2 =$ Me) in 71% yield, presumably by additional alkylation of the allenic nitrile **4a**.[7] Actually the allenic nitrile **4a** (or **4e**) was converted to the allylic nitrile **5a** [or **5b** ($R^1 = R^3 = R^4 = n$-Bu, $R^2 =$ Et)] by reaction with **3a** in 79% (or 87%) yield. On the other hand, use of an excess of higher-order cuprates did not give satisfactory results, with only a mixture of allenic and allylic nitriles being formed in low yields.

Thus, we have developed a convenient method for the synthesis of trisubstituted allenic nitriles from ynone cyano phosphates by reaction with higher-order cuprates.

Experimental

^{1}H-NMR and ^{13}C-NMR spectra were recorded with a Varian Gemini-200 or XL-300 spectrometer; signals are given in ppm. IR spectra were obtained on a Shimadzu IR 435 spectrophotometer. Mass spectra (MS) and high-resolution mass spectra (HRMS) were obtained on a Hitachi M-80 instrument. Bulb-to-bulb distillations were done in a GTO-250R Shibata glass tube oven; boiling points refer to air bath temperature and are uncorrected. For column chromatography, SiO$_2$ (Merck art. 9385) was used. 3-Octyn-2-one (**1a**),[8] 4-nonyn-3-one (**1b**),[8] 4-phenyl-3-butyn-2-one (**1c**),[9] and 2-heptynal (**1d**)[10] were prepared by the literature procedures. 2-Thienyl(cyano)copper lithium was purchased from Aldrich Chemical Company, Inc., as a solution in THF.

General Procedure for the Preparation of Allenic Nitriles 4 A solution of an ynone **1** (0.5 mmol) and DEPC (155 mg, 1.5 mmol) in THF (3 ml) was treated with LiCN (50 mg, 1.5 mmol). The mixture was stirred at room temperature for 10 min, diluted with water (20 ml), then extracted with hexane–EtOAc (1 : 1, 50 ml). The extract was washed with water (2 × 20 ml) and brine (20 ml), dried (Na$_2$SO$_4$), and evaporated *in vacuo* to give the crude cyano phosphate **2**. An n-BuLi 1.6 M hexane solution (0.45 ml, 0.7 mmol) was added to a solution of (2-Th)Cu(CN)Li (0.25 M THF solution) (2.8 ml, 0.7 mmol) in THF (1 ml) under N$_2$ at −78 °C. After being stirred at −30 °C for 20 min, the reaction mixture was cooled again to −78 °C and a solution of the crude cyano phosphate obtained above in THF (3 ml) was added. The whole was stirred at room temperature for 30 min. After cooling to −78 °C, the reaction mixture was quenched by the addition of saturated NH$_4$Cl solution (2 ml) and 10% NH$_4$OH (2 ml), and extracted with ether (50 ml). The extract was washed with brine (20 ml), dried (MgSO$_4$), and evaporated *in vacuo*. The residue was purified by column chromatography with hexane–benzene (1 : 1) to give the allenic nitrile **4** as a colorless oil.

4-Butyl-2-methyl-2,3-octadienenitrile (**4a**): bp 80 °C (0.7 Torr). ^{1}H-NMR (CDCl$_3$) δ: 0.87 (6H, t, $J = 6$ Hz), 1.33 (8H, m), 1.84 (3H, s), 1.99 (4H, t, $J = 7$ Hz). ^{13}C-NMR (CDCl$_3$) δ: 13.94, 17.93, 22.38, 29.47, 32.04, 77.38, 111.16, 117.67, 210.24. IR $\nu_{\max}^{\text{neat}}$ cm^{-1}: 2200, 1950. MS m/z: 191 (M$^+$). HRMS Calcd for C$_{13}$H$_{21}$N: 191.1673. Found: 191.1657. *Anal.* Calcd for C$_{13}$H$_{21}$N: C, 81.67; H, 11.06; N, 7.32. Found: C, 81.86; H, 11.19; N, 7.33.

2-Methyl-4-(1-methylpropyl)-2,3-octadienenitrile (**4b**): bp 75 °C (0.8 Torr). ^{1}H-NMR (CDCl$_3$) δ: 0.88 (6H, m), 1.02, 1.03 (each 3H, each d, $J = 7$ Hz), 1.35 (6H, m), 1.86 (3H, s), 1.98 (3H, s). ^{13}C-NMR (CDCl$_3$) δ: 11.38, 11.44, 13.90, 17.82, 17.90, 18.87, 19.03, 22.40, 27.97, 29.51, 30.01, 30.56, 38.61, 77.86, 115.63, 117.37, 117.43, 209.37. IR $\nu_{\max}^{\text{neat}}$ cm^{-1}: 2220, 1950. MS m/z: 191 (M$^+$). HRMS Calcd for C$_{13}$H$_{21}$N: 191.1673. Found: 191.1672. *Anal.* Calcd for C$_{13}$H$_{21}$N: C, 81.61; H, 11.06; N, 7.32. Found: C, 81.86; H, 11.19; N, 7.33.

2,4-Dimethyl-2,3-octadienenitrile (**4c**): bp 70 °C (1.0 Torr). ^{1}H-NMR (CDCl$_3$) δ: 0.89 (3H, t, $J = 7$ Hz), 1.33 (4H, m), 1.73 (3H, s), 1.85 (3H, s). ^{13}C-NMR (CDCl$_3$) δ: 13.93, 17.94, 18.25, 22.30, 29.29, 33.35, 76.00, 16.19, 117.62, 210.37. IR $\nu_{\max}^{\text{neat}}$ cm^{-1}: 2220, 1960. MS m/z: 149 (M$^+$). HRMS Calcd for C$_{10}$H$_{15}$N: 149.1204. Found: 149.1208. *Anal.* Calcd for C$_{10}$H$_{15}$N: C, 80.48; H, 10.13; N, 9.39. Found: C, 80.27; H, 10.14; N, 9.04.

2-Methyl-4-phenyl-2,3-octadienenitrile (**4d**): bp 150 °C (1.5 Torr). ^{1}H-NMR (CDCl$_3$) δ: 0.93 (3H, t, $J = 7$ Hz), 1.47 (4H, m), 2.0 (1H, s), 2.50 (2H, t, $J = 7$ Hz), 7.35 (5H, s). ^{13}C-NMR (CDCl$_3$) δ: 14.03, 17.94, 22.51, 29.78, 30.02, 80.03, 112.10, 116.70, 127.24, 128.86, 129.28, 134.24, 213.63. IR $\nu_{\max}^{\text{neat}}$ cm^{-1}: 2220, 1940. MS m/z: 211 (M$^+$). HRMS Calcd for C$_{15}$H$_{17}$N: 211.1359. Found: 211.1345. *Anal.* Calcd for C$_{15}$H$_{17}$N: C, 85.26; H, 8.11; N, 6.63. Found: C, 85.43; H, 8.13; N, 6.55.

4-Butyl-2-ethyl-2,3-octadienenitrile (**4e**): bp 85 °C (1.0 Torr). ^{1}H-NMR (CDCl$_3$) δ: 0.88 (6H, t, $J = 7$ Hz), 1.06 (3H, t, $J = 7$ Hz), 1.20—1.40 (8H, m), 2.0 (4H, t, $J = 7$ Hz), and 2.16 (2H, q, $J = 7$ Hz). ^{13}C-NMR (CDCl$_3$) δ: 12.56, 13.99, 22.46, 25.34, 29.60, 32.16, 84.20, 112.40, 117.27, 209.03. IR $\nu_{\max}^{\text{neat}}$ cm^{-1}: 2220, 1950. MS m/z: 205 (M$^+$). HRMS Calcd for C$_{14}$H$_{23}$N: 205.1829. Found: 205.1829. *Anal.* Calcd for C$_{14}$H$_{23}$N: C, 81.29; H, 11.29; N, 6.82. Found; C, 81.54; H, 11.38; N, 7.04.

2-Methyl-4,4-diphenyl-2,3-butadienenitrile (**4f**): ^{1}H-NMR (CDCl$_3$) δ: 2.09 (3H, s), 7.36 (10H, m). ^{13}C-NMR (CDCl$_3$) δ: 17.97, 79.97, 114.86, 115.71, 133.78, 213.83. IR $\nu_{\max}^{\text{neat}}$ cm^{-1}: 2220, 1940. MS m/z: 231 (M$^+$). HRMS Calcd for C$_{17}$H$_{13}$N: 231.1047. Found: 231.1044.

4-Butyl-2,3-octadienenitrile (**4g**): ^{1}H-NMR (CDCl$_3$) δ: 0.88 (6H, t, $J = 7$ Hz), 1.34 (8H, m), 2.0 (4H, m), 5.13 (1H, quint, $J = 3$ Hz). ^{13}C-NMR (CDCl$_3$) δ: 13.79, 22.25, 29.17, 31.41, 67.46, 111.50, 114.62, 213.24. IR $\nu_{\max}^{\text{neat}}$ cm^{-1}: 2220, 1960. MS m/z: 177 (M$^+$). HRMS Calcd for C$_{12}$H$_{19}$N: 177.1517. Found: 177.1517.

3,4-Dibutyl-2-methyl-3-octenenitrile (5a) Method A: An n-BuLi 1.6 M haxane solution (0.96 ml, 1.5 mmol) was added to a suspension of CuI (285 mg, 1.5 mmol) in THF (3 ml) at −30 °C under N$_2$, and the mixture was stirred at −30 °C for 10 min. The reaction mixture was cooled to −78 °C, then a solution of the cyano phosphate of **1a** (62 mg, 0.5 mmol) in THF (2 ml) was added, and the mixture was stirred at room temperature for 30 min. Work-up as described for the preparation of **4** gave a crude oil, which was purified by column chromatography with hexane–benzene (1 : 1) to give **5a** (88 mg, 71%) as a colorless oil, bp 105 °C (1.0 Torr). ^{1}H-NMR (CDCl$_3$) δ: 0.90 (9H, m), 1.28 (12H, m), 1.32 (3H, d, $J = 7$ Hz), 1.90—2.10 (6H, m), 3.64 (1H, q, $J = 7$ Hz). ^{13}C-NMR (CDCl$_3$) δ: 14.02, 14.17, 14.28, 18.90, 22.85, 23.19, 23.42, 28.02, 29.87, 31.09, 31.46, 31.60, 32.13, 32.67, 123.01, 128.83, 139.42. IR $\nu_{\max}^{\text{neat}}$ cm^{-1}: 2240. MS m/z: 249 (M$^+$). HRMS Calcd for C$_{17}$H$_{31}$N: 249.2445. Found: 249.2444. *Anal.* Calcd for C$_{17}$H$_{31}$N: C, 81.85; H, 12.53; N, 5.62. Found; C, 81.74; H, 12.79; N, 5.60.

Method B: By a similar procedure to that described in method A, n-Bu$_2$CuLi (0.7 mmol) was prepared from CuI (133 mg, 0.5 mmol) and n-BuLi (0.45 ml, 0.7 mmol) in THF (3 ml). The reaction mixture was cooled to −78 °C, then a solution of the allenic nitrile **4a** (96 mg, 0.5 mmol) in THF (2 ml) was added, and the mixture was stirred at room temperature for 30 min. Work-up as described for the preparation of **4** gave a crude oil, which was purified by column chromatography with hexane–benzene (1 : 1) to give **5a** (98 mg, 79%). This was identical with **5a** prepared by method A based on a comparison of their IR and ^{1}H-NMR spectra.

3,4-Dibutyl-2-ethyl-3-octenenitrile (5b) By a similar procedure (method B) to that described for the preparation of **5a**, the crude product which was obtained from **4e** (116 mg, 0.5 mmol) and **3a** [prepared from CuI (133 mg, 0.7 mmol) and n-BuLi (0.45 ml, 0.7 mmol)] was purified by column chromatography with hexane–benzene (1 : 1) to give **5b** (114 mg, 87%) as a colorless oil, bp 105 °C (0.4 Torr). ^{1}H-NMR (CDCl$_3$) δ: 0.90 (9H, m), 1.0 (3H, t, $J = 7$ Hz), 1.29 (12H, m), 1.53 (1H, m), 1.80 (1H, m), 1.98 (6H, m), 3.40 (1H, dd, $J = 7$, 9 Hz). ^{13}C-NMR (CDCl$_3$) δ: 12.30, 14.02, 14.17, 23.14, 23.44, 26.43, 30.16, 31.12, 31.39, 31.61, 32.11, 32.60, 35.89, 122.24, 127.65, 140.17. IR $\nu_{\max}^{\text{neat}}$ cm^{-1}: 2240. MS m/z: 263 (M$^+$). HRMS Calcd for C$_{18}$H$_{33}$N: 263.2611. Found: 263.2613. *Anal.* Calcd for C$_{18}$H$_{33}$N: C, 82.06; H, 12.63; N, 5.32. Found: C, 82.00; H, 12.63; N, 5.32.

References and Notes

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