

Consecutive Reaction of Bis[2,2,2-trifluoroethyl] phosphite. One-pot Synthesis of Substituted 3-Cyano- β , γ -unsaturated Nitriles with Exclusive or Predominant *E*-Selectivity[†]

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The consecutive reaction of bis[2,2,2-trifluoroethyl] phosphite and its application to the one-pot synthesis of 3-cyano- β , γ -unsaturated nitriles with exclusive or predominant *E*-selectivity (*E*:*Z* = 100—85:0—15) and excellent yields (94%—99%) are described.

Keywords consecutive reaction, one-pot synthesis, 3-cyano- β , γ -unsaturated nitrile, bis[2,2,2-trifluoroethyl] phosphite, *E*-selectivity

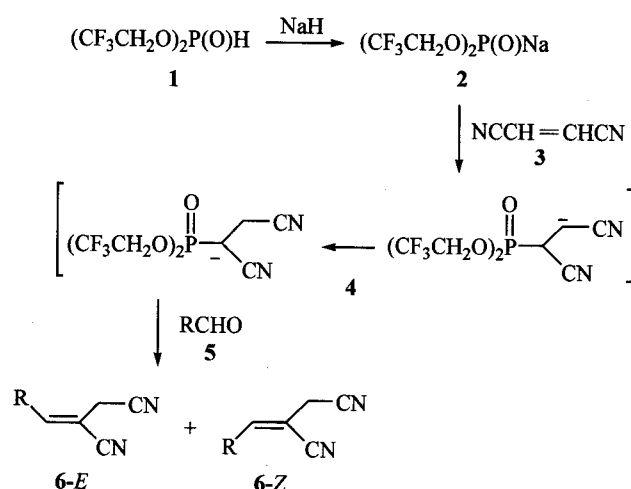
Introduction

Recently 3-cyano- β , γ -unsaturated nitriles have attracted considerable interest¹ and been applied to the [2 + 2] cycloaddition of 1,6-diynes with 1,4-dinitriles catalysed by Ru(II).² The usual methods for their preparation are Wittig or Horner-Wadsworth-Emmons (HWE) reaction which gave a mixture of *Z*- and *E*-isomers of 3-cyano- β , γ -unsaturated nitriles with *Z*-isomer as the major product.³ One-pot three component synthesis of the title compounds also has been reported¹ with modest yields and stereoselectivity. In addition the cyano group is an important functional group for organic transformations.⁴⁻⁷ Therefore, the development of an effective method for the preparation of the title compounds would be valuable.

Results and discussion

As part of our continuing investigation on the synthetic utility of consecutive reaction of organophosphorus compounds in organic synthesis,⁸⁻¹⁷ herein we report the consecutive reaction of bis[2,2,2-trifluoroethyl] phosphite and its application to the one-pot synthesis of 3-cyano- β , γ -unsaturated nitriles with exclusive or predominant *E*-selectivity and excellent yields. The reaction sequence is shown in Scheme 1.

Scheme 1



Treatment of bis[2,2,2-trifluoroethyl] phosphite (1) with sodium hydride in tetrahydrofuran (THF) at 25 °C gave the resulting carbanion 2 which reacted with fumaronitrile (3) forming the intermediate 4. Without isolation 4 reacted with aldehydes, followed by elimination of phosphonate anion, giving substituted 3-cyano- β , γ -unsaturated nitriles with exclusive or predominant *E*-selectivity (*E*:*Z* = 100—85:0—15) in 94%—99% yields. The results are summarized in Table 1.

For the assignment of the configuration of the products we perform the NOESY spectrum of the product of 6a. It showed that the R group is *cis* with respect to the methylene group (*E*-isomer).

In conclusion, this consecutive reaction of bis[2,2,2-trifluoroethyl] phosphite provides a convenient one-pot synthesis of 3-cyano- β , γ -unsaturated nitriles with exclusive or predominant *E*-selectivity and excellent yields. It should be a complement of the existing methods, particu-

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ly for the synthesis of *E*-isomers.

Table 1 Substituted 3-cyano- β , γ -unsaturated nitriles prepared

Compound	R	Yield ^a (%)	Ratio ^b (<i>E</i> : <i>Z</i>)
6a	4-FC ₆ H ₄	94	100:0
6b	4-ClC ₆ H ₄	94	94:6
6c	3-BrC ₆ H ₄	94	94:6
6d	3-CF ₃ OC ₆ H ₄	96	92:8
6e	2,4-Cl ₂ C ₆ H ₃	99	91:9
6f	C ₆ H ₅	98	88:12
6g	4-CH ₃ C ₆ H ₄	99	87:13
6h	4-CH ₃ OC ₆ H ₄	99	85:15

^a Isolated yields; ^b the ratios of *E*- to *Z*-isomers were estimated on the basis of their NMR spectra.

Experimental

All boiling points are uncorrected. The IR spectra of liquid products were determined as films on a Digilab FTS-20E spectrometer. ¹H NMR spectra were recorded on a Bruker AM-300 (300 MHz) spectrometer with TMS as reference and CDCl₃ as solvent, coupling constant (*J*) is in Hz. ¹⁹F NMR spectra were taken on a Varian EM-360 (60 MHz) spectrometer with trifluoroacetic acid as external reference and CDCl₃ was used as solvent (positive for upfield shifts). Mass spectra were measured on a Finnigan GC-MS-4021 mass spectrometer.

Bis(2,2,2-trifluoroethyl)phosphite (**1**) was prepared according to the known method¹⁸.

General procedure for the synthesis of 3-cyano- β , γ -unsaturated nitriles **6**

Bis(2,2,2-trifluoroethyl)phosphite (2.5 mmol) was added slowly with stirring to a suspension of sodium hydride [60% NaH, 0.1 g, 2.5 mmol] in tetrahydrofuran (THF, 20 mL) at 20 °C under nitrogen. After being stirred for 0.5 h at 20 °C, fumaronitrile (0.20 g, 2.5 mmol) was slowly added. The mixture was further stirred for 0.5 h and the aldehyde (2 mmol) was added. After addition the mixture was stirred for further 3 h and quenched with HCl solution (2 mol · L⁻¹, 30 mL). The reaction mixture was extracted with ethyl acetate (3 × 20 mL), washed with brine (20 mL) and dried over anhydrous Na₂SO₄. Evaporation of the solvent gave a residue, which was purified by flash chromatography on silica gel eluting with light petroleum ether (b.p. 60–90 °C)-ethyl acetate (10:1, *V*:*V*) to give the product **6**.

(*E*)-4-(4-Fluorophenyl)-3-cyano-but-3-enenitrile (**6a**) Oil, ¹H NMR (CDCl₃, 300 MHz) δ : 3.50 (s, 2H), 7.15–7.40 (m, 2H), 7.30–7.38 (m, 2H), 7.49 (s, 1H); IR (film) ν : 2260, 2210, 1630, 1600, 1510, 1240 cm⁻¹; MS (70 eV) *m/z* (%): 186 (M⁺, 100), 159 (75), 158 (64), 132 (20), 109 (27). Anal. calcd for C₁₁H₇FN₂ (186.20): C 70.96, H 3.79, N 15.05; found C 71.06, H 3.70, N 15.29.

4-(4-Chlorophenyl)-3-cyano-but-3-enenitrile (**6b**) Oil, *E*:*Z* = 94:6; ¹H NMR (CDCl₃, 300 MHz) δ : 3.48 (s, 0.94 × 2H, *E*), 3.53 (s, 0.06 × 2H, *Z*), 7.26 (d, *J* = 8.4 Hz, 0.94 × 2H, *E*), 7.46 (s, 1H), 7.47 (d, *J* = 8.4 Hz, 2H), 7.71 (d, *J* = 7.2 Hz, 0.06 × 2H, *Z*); IR (film) ν : 2250, 2210, 1630, 1590, 1490, 1430 cm⁻¹; MS (70 eV) *m/z* (%): 204 (M⁺ + 2, 25), 202 (M⁺, 67), 167 (35), 140 (100), 125 (14). Anal. calcd for C₁₁H₇ClN₂ (202.64): C 65.20, H 3.48, N 13.82; found C 65.14, H 3.34, N 13.80.

4-(3-Bromophenyl)-3-cyano-but-3-enenitrile (**6c**) B.p. 150 °C/0.65 × 10² Pa, *E*:*Z* = 94:6; ¹H NMR (CDCl₃, 300 MHz) δ : 3.51 (s, 0.94 × 2H, *E*), 3.56 (s, 0.06 × 2H, *Z*), 7.26 (s, 17H), 7.36–7.40 (m, 1H), 7.45–7.46 (m, 2H), 7.58–7.62 (m, 1H); IR (film) ν : 2240, 2220, 1610, 1580, 1490, 1220 cm⁻¹; MS (70 eV) *m/z* (%): 248 (M⁺ + 2, 31), 246 (M⁺, 31), 167 (20), 140 (100). Anal. calcd for C₁₁H₇BrN₂ (247.09): C 53.47, H 2.86, N 11.34; found C 53.41, H 2.79, N 11.25.

4-(3-Trifluoromethoxyphenyl)-3-cyano-but-3-enenitrile (**6d**) B.p. 130 °C/0.65 × 10² Pa, *E*:*Z* = 92:8; ¹H NMR (CDCl₃, 300 MHz) δ : 3.50 (s, 0.92 × 2H, *E*), 3.56 (s, 0.08 × 2H, *Z*), 7.16 (s, 1H), 7.25–7.33 (m, 2H), 7.45–7.70 (m, 2H); ¹⁹F NMR (CDCl₃/TFA, 60 MHz) δ : -20.0 (s, 3F); IR (film) ν : 2240, 2220, 1580, 1490, 1260 cm⁻¹; MS (70 eV) *m/z* (%): 252 (M⁺, 100), 225 (19), 204 (9), 166 (30), 175 (8), 155 (18), 139 (45), 128 (23). Anal. calcd for C₁₂H₇F₃N₂O (252.19): C 57.15, H 2.80, N 11.11; found C 57.12, H 2.67, N 11.06.

4-(2,4-Dichlorophenyl)-3-cyano-but-3-enenitrile (**6e**) Oil, *E*:*Z* = 91:9; ¹H NMR (CDCl₃, 300 MHz) δ : 3.38 (s, 0.91 × 2H, *E*), 3.57 (s, 0.09 × 2H, *Z*), 7.20–7.26 (m, 0.91 (1H, *E*), 7.37–7.44 (m, 0.91 × 1H, *E*), 7.50 (m, 0.09 × 1H, *Z*), 7.53 (s, 1H), 7.54–7.56 (m, 0.91 × 1H, *E*), 7.61–7.63 (m, 0.09 × 1H, *Z*), 7.88–7.92 (m, 0.09 × 1H, *Z*); IR (film) ν : 2250, 2220, 1630, 1590, 1560, 1380 cm⁻¹; MS (70 eV) *m/z* (%): 240 (M⁺ + 4, 31), 238 (M⁺ + 2, 65), 236 (M⁺, 91), 201 (51), 174 (100), 165 (39), 159 (23). Anal. calcd for C₁₁H₆Cl₂N₂ (237.08): C 55.73, H 2.55, N 11.82; found C 55.64, H 2.37, N 11.82.

4-(Phenyl)-3-cyano-but-3-enenitrile (**6f**) Oil, *E*:*Z* = 89:11; ¹H NMR (CDCl₃, 300 MHz) δ : 3.50 (s, 0.89 × 2H, *E*), 3.53 (s, 0.11 × 2H, *Z*), 7.31–7.34 (m, 0.89 × 2H, *E*), 7.48 (s, 1H), 7.50–7.58 (m, 3H), 7.80–7.86 (m, 0.11 × 2H, *Z*); IR (film) ν : 2250, 2220, 1620, 1500, 1450 cm⁻¹; MS (70 eV) *m/z* (%): 169 (M⁺ + 1, 45), 168 (M⁺, 100), 142 (20), 141 (58), 140 (44). Anal. calcd for C₁₁H₈N₂ (168.19): C 78.55, H 4.79, N 16.66; found C 78.66, H 4.73, N 16.79.

4-(4-Methylphenyl)-3-cyano-but-3-enenitrile (**6g**) Oil, *E*:*Z* = 88:12; ¹H NMR (CDCl₃, 300 MHz) δ : 2.41 (s, 3H), 3.51 (s, 2H), 7.22 (d, *J* = 8.4 Hz,

0.88 × 2H, *E*), 7.26—7.30 (m, 2H), 7.46 (s, 1H), 7.68 (d, *J* = 8.1 Hz, 0.12 × 2H, *Z*); IR (film) ν : 2250, 2210, 1610, 1510, 1420 cm^{-1} ; MS (70 eV) *m/z* (%): 182 (M^+ , 100), 181 (66), 154 (46), 140 (52), 128 (18), 115 (22). Anal. calcd for $\text{C}_{12}\text{H}_{10}\text{N}_2$ (182.22): C 79.10, H 5.53, N 15.37; found C 79.16, H 5.54, N 15.42.

4-(4-Methoxyphenyl)-3-cyano-but-3-enenitrile (**6h**)
Oil, *E*:*Z* = 83:17; ^1H NMR (CDCl_3 , 300 MHz) δ : 3.49 (s, 0.17 × 2H, *Z*), 3.51 (s, 0.83 × 2H, *Z*), 3.87 (s, 3H), 6.90—7.00 (m, 2H), 7.25—7.36 (m, 0.83 × 2H, *E*), 7.42 (s, 1H), 7.71—7.80 (m, 0.17 × 2H, *Z*); IR (film) ν : 2250, 2210, 1600, 1570, 1510, 1260 cm^{-1} ; MS (70 eV) *m/z* (%): 198 (M^+ , 100), 183 (15), 171 (11), 155 (31), 128 (29), 121 (23). Anal. calcd for $\text{C}_{12}\text{H}_{10}\text{N}_2\text{O}$ (198.22): C 72.71, H 5.08, N 14.13; found C 72.60, H 4.97, N 14.24.

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