J. Chem. Research (S), 1999, 556–557†

HMPA Promoted Sequential Transformations of Phosphonates. Highly Stereoselective Synthesis of (*E*)-4-Ethoxycarbonyl-γ,δ-unsaturated Nitriles†

Yanchang Shen* and Zhenghong Zhang

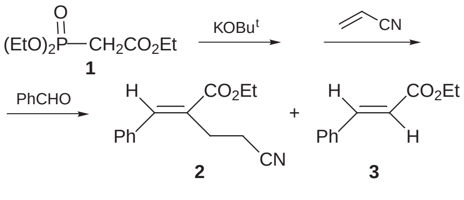
Shanghai Institute of Organic Chemistry, Academia Sinica 354 Fenglin Lu, Shanghai 200032, China

The HMPA promoted sequential transformations of diethyl ethoxycarbonyl phosphonate with potassium *tert*-butoxide, acrylonitrile and aldehydes affords 4-ethoxycarbonyl-(*E*)-γ,δ-unsaturated nitriles in 71–86% yields.

The reactions of phosphoryl-stabilized carbanions with aldehydes or ketones are known as Horner–Wadsworth–Emmons (HWE) reactions and have been investigated extensively.[1] Vinylphosphonates undergo Michael addition of nucleophiles to generate phosphoryl-stabilized carbanions which readily react with carbonyl compounds to afford olefination products, heterocyclic or carbocyclic compounds.[2] However the Michael-type addition reaction of phosphoryl-stabilized carbanions to unsaturated compounds is still limited.[3] After Michael-type addition and abstraction of a proton it provides a methodology for the preparation of compounds bearing a phosphonate moiety.[3,4] Sequential transformations have attracted much interest in recent years because they provide a simple and efficient entry to complex compounds by including two or more transformations in a single operation to increase the complexity of substrate, starting from commercially available, relatively simple precursors.[5] Recently, consecutive reactions of phosphonates have attracted much interest and have been applied to the synthesis of primary (*E*)-allylic amines.[6]

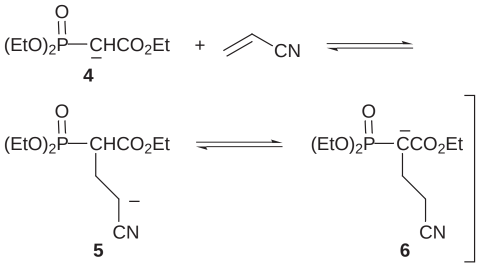
The title compounds **7** are 1,5-bifunctional compounds which are a useful class of substrates in aldol-type condensation and other annulation reactions.[7] Therefore development of an effective method for their preparation would be valuable.

In our continuing investigation, the synthetic application of sequential transformation of phosphonates for the synthesis of perfluoroalkylated α-fluoro-α,β-unsaturated esters,[8] perfluoroalkylated 4-cyanoalka-1,4-dienes,[9] perfluoroalkylated α,β-unsaturated nitriles,[10] tetrasubstituted perfluoroalkylated (*Z*)-α,β-unsaturated esters[11] and trifluoromethylated 1,3-butadienylphosphonates[12] which would be difficult to prepare otherwise, we attempted the following reaction (Scheme 1).



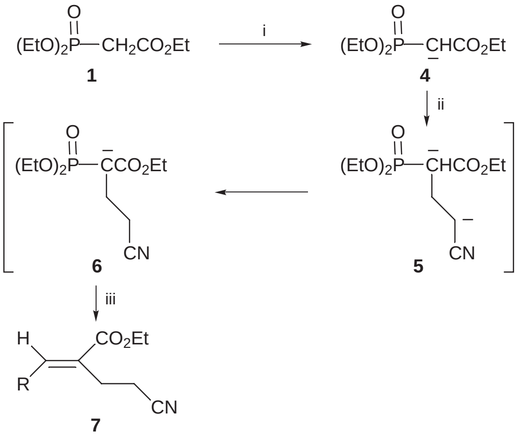
Scheme 1

The desired product **2** was obtained in 44% yield but was contaminated with a 43% yield of ethyl *trans*-cinnamate **3**. It seems that there is a dynamic equilibrium between the phosphoryl-stabilized carbanion and the adduct (Scheme 2). Thus, benzaldehyde reacted with **6** to give **2** and with **4** to give **3**. Fortunately we found that the HMPA (hexamethylphosphoramide) could promote this consecutive reaction and the desired product was obtained exclusively.



Scheme 2

The phosphoryl-stabilized carbanions **4**, generated from the corresponding phosphonate and potassium *tert*-butoxide in tetrahydrofuran (THF) were reacted with acrylonitrile promoted by hexamethylphosphoramide (HMPA) to give the Michael addition adduct **5**, which was converted to **6** *via* proton-transfer. Then **6** reacted with aldehydes to give the products **7** exclusively as (*E*) isomers in 71–86% yield (Scheme 3). The results are summarized in Table 1.



Scheme 3 *Reagents and conditions*: i, $KOBu^t$, THF 20 °C, 0.5 h; ii, HMPA, acrylonitrile, 20 °C, 2 h; iii, RCHO, 20 °C, 3 h

For the assignment of the configuration of products we performed NOESY spectroscopy for **7a**. It shows that the 4-fluorophenyl is *cis* with respect to the CH_2CH_2CN group. Thus the geometry of the newly formed double bond in products are exclusively (*E*).

Unfortunately, the HMPA promoted sequential transformations of diethyl (ethoxycarbonyl)phosphonate with potassium *tert*-butoxide, methyl acrylate and aldehydes

---

* To receive any correspondence.

† This is a **Short Paper** as defined in the Instructions for Authors, Section 5.0 [see *J. Chem. Research (S)*, 1999, Issue 1]; there is therefore no corresponding material in *J. Chem. Research (M)*.

Table 1 Preparation of 4-ethoxycarbonyl-(*E*)-γ,δ-unsaturated nitriles

Compound	R	Yield(%)[a]
7a	4-FC_6H_4	83
7b	4-ClC_6H_4	81
7c	4-$CH_3OC_6H_4$	71
7d	4-$CH_3C_6H_4$	81
7e	4-$NO_2C_6H_4$	71
7f	Ph	85
7g	2-Furyl	79
7h	*E*-$C_6H_5CH{=}CH$	86

[a] Isolated yields.

was unsuccessful under same conditions. Presently the other conditions for this sequential transformation are being pursued.

HMPA is a highly polar, aprotic solvent and is frequently used to accelerate organolithium reactions.[14] The ability of HMPA to alter conjugate addition of lithium carbanions to α,β-enones has been noted.[13] However to the best of our knowledge HMPA promoted sequential transformations have not been reported previously.

In conclusion, this methodology provides a convenient and highly stereoselective synthesis of the title compounds with (*E*)-isomers formed exclusively from commercially available substances. They would be expected to be useful intermediates in organic synthesis, particularly in annulation reactions.

Experimental

Mps are uncorrected. The IR spectra of solid products were obtained as KCl disks and of liquid products as films on a Digilab FTS-20E spectrometer. ^1H NMR spectra were recorded on a Bruker AM-300 (300 MHz) spectrometer (δ values in ppm from $SiMe_4$, in $CDCl_3$, J values are given in Hz). Mass spectra were measured on a Finnigan GC-MS-4021 mass spectrometer.

General Procedure for the Preparation of 4-Ethoxycarbonyl-(E)-γ,δ-Unsaturated Nitriles.—A mixture of diethyl (ethoxycarbonylmethyl)phosphonate (0.448 g, 2 mmol), potassium *tert*-butoxide (0.224 g, 2 mmol) and THF (10 cm^3) at 20 °C under nitrogen was stirred for 0.5 h. Then HMPA (0.71 g, 4 mmol) and acrylonitrile (0.106 g, 2 mmol) were added in turn. Stirring was continued at 20 °C for 2 h, after which aldehyde (2 mmol) was added dropwise to the mixture which was stirred at 20 °C for 3 h until the disappearance of aldehyde (shown by TLC). The reaction mixture was acidified with 1 ml of 1 M HCl, concentrated and water (20 cm^3) added. The aqueous layer was extracted with diethyl ether (3×20 cm^3). The combined organic layer was washed with brine (3×10 cm^3) until neutral and dried over Na_2SO_4. Evaporation of the solvent gave a residue which was purified by column chromatography eluting with light petroleum (60–90 °C)–ethyl acetate (20:1) to give the product **7**.

4-*Ethoxycarbonyl*-5-(4-*fluorophenyl)pent*-4-*enenitrile* (**7a**).—Yield: 83%, oil. ν_{max}/cm^{-1}: 2250, 1700, 1630. δ_H 7.83 (s, 1H), 7.35 (dd, 2H, $J = 8.5$, 5.5 Hz), 7.08 (t, 2H, $J = 8.6$ Hz), 4.30 (q, 2H, $J = 7.1$ Hz), 2.85 (t, 2H, $J = 7.4$ Hz), 2.64 (t, 2H, $J = 7.4$ Hz), 1.36 (t, 3H, $J = 7.1$ Hz); m/z 248 ($M^+ + 1$, 23), 247 (M^+, 50), 218 (22), 202 (65), 133 (100) (Found: C, 67.88; H, 5.65; N, 5.22. $C_{14}H_{14}FNO_2$ requires C, 68.00; H, 5.71; N, 5.66%).

The NOESY spectrum shows that the 4-fluorophenyl is *cis* with respect to the CH_2CH_2CN group.

4-*Ethoxycarbonyl*-5-(4-*chlorophenyl)pent*-4-*enenitrile* (**7b**). Yield: 81%, mp 45 °C, ν_{max}/cm^{-1}: 2240, 1700, 1630. δ_H 7.82 (s, 1H), 7.24–7.42 (m, 4H), 4.30 (q, 2H, $J = 7.1$ Hz), 2.84 (t, 2H, $J = 7.3$ Hz), 2.64 (t, 2H, $J = 7.3$ Hz), 1.36 (t, 3H, $J = 7.1$ Hz); m/z 264 ($M^+ + 1$, 13), 236 (M^+, 72), 234 (31), 223 (36), 151 (100), 115 (88) (Found: C, 63.53; H, 5.43; N, 5.19. $C_{14}H_{14}ClNO_2$ requires C, 63.76; H, 5.35; N, 5.31%).

4-*Ethoxycarbonyl*-5-(4-*methoxyphenyl)pent*-4-*enenitrile* (**7c**). Yield: 71%, mp 60 °C. ν_{max}/cm^{-1}: 2250, 1710, 1600. δ_H 7.80 (s, 1H), 7.32 (d, 2H, $J = 8.8$ Hz), 6.95 (d, 2H, $J = 8.7$ Hz), 4.29 (q, 2H, $J = 7.1$ Hz), 3.84 (s, 3H), 2.92 (t, 2H, $J = 7.6$ Hz), 2.63 (t, 2H, $J = 7.6$ Hz), 1.35 (t, 3H, $J = 7.1$ Hz). m/z 260 (M^++1, 12), 259 (M^+, 64), 219 (54), 173 (26), 145 (100) (Found: C, 69.37; H, 6.54; N, 5.26. $C_{15}H_{17}NO_3$ requires C, 69.48; H, 6.61; N, 5.40%).

4-*Ethoxycarbonyl*-5-(4-*methylphenyl)pent*-4-*enenitrile* (**7d**). Yield: 81%, oil. ν_{max}/cm^{-1}: 2250, 1700, 1630. δ_H 7.84 (s, 1H), 7.20–7.33 (m, 4H), 4.30 (q, 2H, $J = 7.1$ Hz), 2.90 (t, 2H, $J = 7.5$ Hz), 2.62 (t, 2H, $J = 7.4$ Hz), 2.38 (s, 3H), 1.36 (t, 3H, $J = 7.1$ Hz); m/z 244 (M^++1, 18), 243 (M^+, 100), 203 (29), 157 (22), 129 (57) (Found: C, 73.72; H, 7.14; N, 5.33. $C_{15}H_{17}NO_2$ requires C, 74.05; H, 7.04; N, 5.76%).

4-*Ethoxycarbonyl*-5-(4-*nitrophenyl)pent*-4-*enenitrile* (**7e**). Yield: 71%, mp 85 °C. ν_{max}/cm^{-1}: 2240, 1710, 1630. δ_H 8.30 (d, 2H, $J = 8.8$ Hz), 7.92 (s, 1H), 7.55 (d, 2H, $J = 8.8$ Hz), 4.31 (q, 2H, $J = 7.1$ Hz), 2.80 (t, 2H, $J = 7.5$ Hz), 2.67 (t, 2H, $J = 7.4$ Hz), 1.38 (t, 3H, $J = 7.1$ Hz); m/z 274 (M^+, 21), 245 (100), 229 (52), 188 (40), 115 (79) (Found: C, 60.93; H, 5.10; N, 9.83. $C_{14}H_{14}N_2O_4$ requires C, 61.30; H, 5.14; N, 10.20%).

4-*Ethoxycarbonyl*-5-*phenylpent*-4-*enenitrile* (**7f**). Yield: 85%, oil. ν_{max}/cm^{-1}: 2250, 1730, 1630. δ_H 7.88 (s, 1H), 7.25–7.46 (m, 5H), 4.29 (q, 2H, $J = 7.1$ Hz), 2.98 (t, 2H, $J = 7.4$ Hz), 2.63 (t, 2H, $J = 7.5$ Hz), 1.36 (t, 3H, $J = 7.1$ Hz); m/z 230 ($M^+ + 1$, 46), 229 (M^+, 54), 200 (36), 184 (100), 143 (29), 115 (81) (Found: C, 72.98; H, 6.52; N, 5.96. $C_{14}H_{15}NO_2$ requires C, 73.34; H, 6.59; N, 6.11%).

4-*Ethoxycarbonyl*-5-(2-*furyl)pent*-4-*enenitrile* (**7g**). Yield: 79%, mp 50 °C. ν_{max}/cm^{-1}: 2250, 1760, 1690. δ_H 7.59 (d, 1H, $J = 1.5$ Hz), 7.48 (s, 1H), 6.67 (d, 1H, $J = 3.3$ Hz), 6.52 (dd, 1H, $J = 1.6$, 3.4 Hz), 4.25 (q, 2H, $J = 7.2$ Hz), 3.15(t, 2H, $J = 7.5$ Hz), 2.59 (t, 2H, $J = 7.6$ Hz), 1.34 (t, 3H, $J = 7.1$ Hz); m/z 219 (M^+, 90), 179 (71), 174 (100), 151 (64), 105 (31) (Found: C, 65.73; H, 6.23; N, 6.31. $C_{12}H_{13}NO_3$ requires C, 65.74; H, 5.98; N, 6.39%).

4-*Ethoxycarbonyl*-5-*phenylhept*-4-*enenitrile* (**7h**). Yield: 86%, mp 55 °C. ν_{max}/cm^{-1}: 2250, 1690, 1620. δ_H 7.50–7.55 (m, 3H), 7.32–7.36 (m, 3H), 7.08 (dd, 1H, $J = 15.2$, 10.6 Hz), 6.99 (d, 1H, $J = 15.2$ Hz), 4.27 (q, 2H, $J = 7.1$ Hz), 2.87 (t, 2H, $J = 7.3$ Hz), 2.60 (t, 2H, $J = 7.4$ Hz), 1.35 (t, 3H, $J = 7.1$ Hz); m/z 255 (M^+, 46), 210 (23), 169 (59), 141 (100), 115 (30) (Found: C, 75.05; H, 6.79; N, 5.35. $C_{16}H_{17}NO_2$ requires C, 75.27; H, 6.71; N, 5.49%).

We thank the National Natural Science Foundation of China, the Laboratory of Organometallic Chemistry, and Academia Sinica for financial support.

Received, 30th March 1999; Accepted, 27th May 1999
Paper E/9/02557J

References

1 B. E. Maryanoff and A. B. Reitz, *Chem. Rev.*, 1989, **89**, 863.
2 T. Minami and J. Motoyoshiya, *Synthesis*, 1992, 333.
3 S. M. Ruder and V. R. Kulkarni, *J. Chem. Soc., Chem. Commun.*, 1994, 2119 and references cited therein.
4 T. Yamaguchi, Y. Tsukamoto, A. Hayashi and T. Minami, *Tetrahedron Lett.*, 1990, **31**, 2423; R. M. Davidson and G. L. Kenyon, *J. Org. Chem.*, 1990, **55**, 2698; C. Yuan, C. Li and Y. Ding, *Synthesis*, 1991, 854.
5 L. F. Tietze and U. Beifuss, *Angew. Chem., Int. Ed. Engl.*, 1993, **32**, 131; A. Padwa. E. A. Curtis and V P. Sandanayaka, *J. Org. Chem.*, 1996, **61**, 73; L. F. Tietze, *Chem. Rev.*, 1996, **96**, 115; P. J. Parsons, C. S. Penkett and A. J. Shell, *Chem. Rev.*, 1996, **96**, 195.
6 W. S. Shin, K. Lee and D. Y. Oh, *Tetrahedron Lett.*, 1995, **36**, 281.
7 C. S. Yi and N. Liu, *J. Organomet. Chem.*, 1998, **553**, 157 and references cited therein.
8 Y. Shen and J. Ni, *J. Org. Chem.*, 1997, **62**, 7260.
9 Y. Shen and J. Ni, *J. Chem. Res. (S)*, 1997, 358.
10 Y. Shen and J. Ni, *J. Fluorine Chem.*, 1997, **86**, 173.
11 Y. Shen and J. Ni, *J. Fluorine Chem.*, 1998, **89**, 141.
12 Y. Shen, P. Li, J. Ni and J. Sun, *J. Org. Chem.*, 1998, **63**, 9369.
13 H. J. Reich and W. H. Sikorski, *J. Org. Chem.*, 1999, **64**, 14 and references cited therein.