A Novel Synthesis of β-Perfluoroalkylated α,β-Unsaturated Nitriles

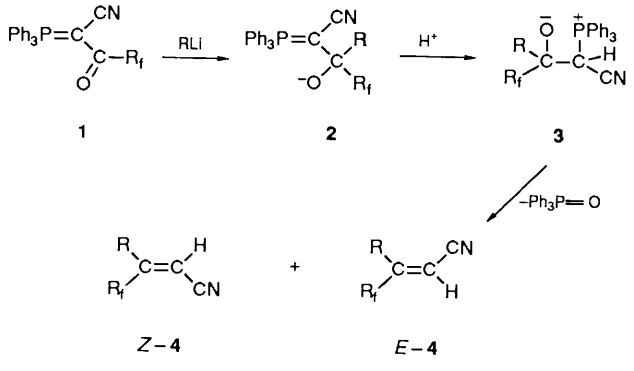
Yanchang Shen * and Tielin Wang
Shanghai Institute of Organic Chemistry, Academia Sinica 345 Lingling Lu, Shanghai 200032, China

A novel intramolecular Wittig reaction proceeding *via* ylide-anion formation and protonation and its application to the synthesis of β-perfluoroalkyl-α,β-unsaturated nitriles is described.

α,β-Unsaturated nitriles and their fluoro species have much potential, particularly in the synthesis of biologically active compounds, since they can serve as useful intermediates and undergo many organic transformations.[1] However, to the best of our knowledge, the synthesis of β-perfluoroalkyl-α,β-unsaturated nitriles has not been reported.

Perfluoroacylmethylenetriphenylphosphoranes were found to be very stable and did not react with aldehydes because of the strong electron-withdrawing effect of the perfluoroacyl groups; only the intramolecular Wittig reaction occurred, at 250 °C, giving fluoro acetylenes.[2] We recently reported an ylide-anion formation resulting from nucleophilic addition to the β-perfluoroacyl group to activate trifluoroacetylmethylenetriphenylphosphorane and its application to the synthesis of α-trifluoromethyl *trans*-allylic alcohols.[3] We now wish to report a novel intramolecular Wittig reaction proceeding *via* ylide-anion formation resulting from nucleophilic addition and protonation and its application to the synthesis of β-perfluoro-α,β-unsaturated nitriles.

The nucleophilic reagents could regiospecifically attack the perfluoroacyl group of perfluoroacylcyanomethylenetriphenylphosphorane **1** to form ylide-anion **2** and, after protonation with acetic acid, the intramolecular Wittig reaction occurred spontaneously to give product **4** in 90–96% yield. The *E* and *Z* isomers of **4** could be separated conveniently by column



chromatography on silica gel and *E* isomers were the major products (86–100%). The results are shown in Table 1. All products are new and characterized by microanalyses, IR, NMR and mass spectroscopy.

It is noteworthy that this reaction is of wide scope; the R groups may be aryl, alkynyl or heterocyclic. The nucleophilic attack was regiospecific at the perfluoroacyl groups while the cyano group was not attacked. When the alkynyl lithium was used as the nucleophilic reagent, a 1-cyano-2-en-4-yne was obtained. The synthesis of fluorine-containing conjugated enyne is not easy,[4] therefore, this new methodology should be useful in the synthesis of biologically active compounds.

Experimental

The general procedure was as follows: lithium reagent (4 mmol) was added dropwise with stirring to a solution of ylide **1** (4 mmol) in dry THF (16 ml) at −60 or 0 °C under nitrogen. The reaction mixture was stirred for 1 h at the same temperature, forming ylide-anion **2**, and acetic acid (1 ml) was added. The mixture was warmed to 20 °C, stirred for 2 h and diethyl ether (20 ml) was added. The organic layer was washed repeatedly with water to neutral pH and dried. Evaporation of the solvent gave a residue which was separated by a column chromatography on silica gel eluting with light petroleum (b.p. 60–90 °C)–ethyl acetate (97:3) to afford product **4**.

Table 1 Synthesis of compounds **4**

4	R	R_f	t^a/°C	Yield[b]	*E*:*Z*[b]
a	Ph	CF_3	−60	91	88:12
b	Ph	n-C_3F_7	−60	90	87:13
c	2-thienyl	CF_3	0	90	100:0
d	2-thienyl	n-C_3F_7	0	96	100:0
e	PhC≡C	CF_3	0	98	92:8
f	PhC≡C	n-C_3F_7	0	93	95:5
g	hex-1-ynyl	CF_3	0	90	86:14
h	hex-1-ynyl	n-C_3F_7	0	93	87:73

[a] Reaction temperature of **1** with RLi. [b] Isolated results.

4,4,4-*Trifluoro*-3-*phenylbut*-2-*enenitrile* **4a**.—*E* isomer, b.p. 110 °C/2 mmHg; ν_{max}/cm^{-1} 2190, 1620 and 845; δ_H 7.56 (5 H, m) and 6.16 (1 H, s); δ_F(TFA$_{ext}$) −10.9 (s, 3 F).

Z isomer, b.p. 105 °C/2 mmHg; ν_{max}/cm^{-1} 2170, 1610 and 845; δ_H 7.46 (5 H, m) and 5.90 (1 H, s); δ_F −15.6 (3 F, s).

m/*z* 197 (M^+), 170 and 128 (Found: C, 60.85; H, 3.03; N, 7.17. $C_{10}H_6F_3N$ requires C, 60.92; H, 3.07; N, 7.10%).

4,4,5,5,6,6,6-*Heptafluoro*-3-*phenylhex*-2-*enenitrile* **4b**.—*E* isomer, b.p. 110 °C/2 mmHg; ν_{max}/cm^{-1} 2160, 1620 and 845; δ_H 7.45 (5 H, m) and 6.06 (1 H, s); δ_F 3.6 (3 F, s), 35.4 (2 F. s) and 47.5 (2 F, s).

Z isomer, b.p. 105 °C/2 mmHg; ν_{max}/cm^{-1} 2160, 1610 and 845; δ_H 7.40 (5 H, m) and 5.86 (1 H, s); δ_F 3.1 (3 F, s), 32.0 (2 F, m) and 47.5 (2 F, s).

m/*z* 297 (M^+), 178 and 128 (Found: C, 48.94; H, 1.87; N, 4.70. $C_{12}H_6F_7N$ requires C, 48.50; H, 2.03; N, 4.71%).

4,4,4-*Trifluoro*-3-(2-*thienyl*)*but*-2-*enenitrile* **4c**.—*E* isomer, b.p. 105 °C/2 mmHg; ν_{max}/cm^{-1} 2160, 1600 and 846; δ_H 7.36–7.76 (2 H, m), 6.96–7.16 (1 H, m) and 5.86 (1 H, m); δ_F −12.0 (3 F, s); *m*/*z* 203 (M^+), 135 and 134 (Found: C, 47.35; H, 1.93; N, 6.98. $C_8H_4F_3NS$ requires C, 47.29; H, 1.98; N, 6.98%).

4,4,5,5,6,6,6-*Heptafluoro*-3-(2-*thienyl*)*hex*-2-*enenitrile* **4d**.—*E* isomer, b.p. 115 °C/2 mmHg; ν_{max}/cm^{-1} 2160, 1590 and 800; δ_H 7.35–7.73 (2 H, m), 6.93–7.20 (1 H, m) and 5.93 (1 H, s); δ_F 3.6 (3 F, s), 34.3 (2 F, s) and 47.3 (2 F, s); *m*/*z* 303 (M^+), 184 and 134 (Found: C, 39.78; H, 1.30; N, 4.78. $C_8H_4F_3NS$ requires C, 39.61; H, 1.33; N, 4.62%).

3-*Trifluoromethyl*-5-*phenyl*-*pent*-2-*en*-4-*ynenitrile* **4e**.—*E* isomer, b.p. 120 °C/2 mmHg; ν_{max} 2150, 2200, 1600 and 815; δ_H 7.22 (5 H, m), 5.93 (1 H, s); δ_F −9.2 (3 F, s).

Z isomer, b.p. 127 °C/2 mmHg; ν_{max}/cm^{-1} 2140 and 850; δ_H 7.30 (5 H, m), 5.78 ppm (1 H, s); δ_F −12.7 ppm (3 F, s).

m/z 221 (M^+) and 152 (Found: C, 64.98; H, 2.73; N, 6.45. $C_{12}H_6F_3N$ requires C, 65.16; H, 2.73; N, 6.33%).

4,4,5,5,6,6,6-*Heptafluoro*-3-(*phenylethynyl*)*hex*-2-*enenitrile* **4f**.—*E* isomer, b.p. 150 °C/2 mmHg; ν_{max}/cm^{-1} 2150 and 810; δ_H 7.33 (5 H, m) and 6.00 (1 H, s); δ_F 3.4 (3 F, s), 35.6 (2 F, s) and 48.3 (2 F, s).

Z isomer, b.p. 159 °C/2 mmHg; ν_{max}/cm^{-1} 2150 and 850; δ_H 7.37 (5 H, m) and 580 (1 H, s); δ_F 3.0 (3 F, s), 31.9 (2 F, s), 48.2 (2 F, s).

m/z 321 (M^+), 202 and 152 (Found C, 51.94; 2.07; N, 4.40. $C_{14}H_6F_7N$ requires C, 52.31; H, 1.88; N, 4.36%).

3-*Trifluoromethylnon*-2-*en*-4-*ynenitrile* **4g**.—*E* isomer, b.p. 86 °C/2 mmHg; ν_{max}/cm^{-1} 2150, 1600 and 830; δ_H 6.07 (1 H, s), 2.55 (2 H, t, *J* 6.0 Hz), 1.60 (4 H, m) and 0.85 (3 H, t); δ_F −9.0 (3 F, m).

Z isomer, b.p. 92 °C/2 mmHg; ν_{max}/cm^{-1} 2150, 1600 and 820; δ_H 5.85 (1 H, s), 2.75 (2 H, t, *J* 6 Hz), 1.60 (4 H, m) and 0.85 (3 H, t); δ_F −12.3 (3 F, s).

m/z 201 (M^+), 200, 183, 159 and 132 (Found: C, 58.96; H, 4.81; N, 6.85. $C_{10}H_{10}F_3N$ requires C, 59.69; H, 5.01; N, 6.96%).

3-(1,1,2,2,3,3,3-*Heptafluoropropyl*)*non*-2-*en*-4-*ynenitrile* **4h**.—*E* isomer, b.p. 110 °C/2 mmHg; ν_{max}/cm^{-1} 2170, 1590 and 805; δ_H 6.00 (1 H, s), 2.45 (2 H, m), 1.45 (4 H, m) and 0.87 (3 H, t); δ_F 3.3 (3 F, s), 35.6 (2 F, m) and 49.0 (2 F, s).

Z isomer, b.p. 120 °C/2 mmHg; ν_{max}/cm^{-1} 2150, 1590 and 830; δ_H 5.87 (1 H, s), 2.40 (t, *J* 6.0 Hz), 1.50 (4 H, m), 0.87 (3 H, t); δ_F 3.0 (3 F, s), 33.3 (2 F, s) and 48.4 (2 F, s).

m/z 301 (M^+), 300, 286, 259 and 182 (Found: C, 48.37; H, 3.36; N, 4.63. $C_{12}H_{10}F_7N$ requires C, 47.85; H, 3.34; N, 4.65%).

Acknowledgements

The authors thank the National Natural Science Foundation of China and Academia Sinica for financial support.

References

1 P. P. Bay, G. Gerbart, V. van Dorsselaer and C. Danzin, *J. Med. Chem.*, 1983, **26**, 1551; R. S. H. Liu, H. Matsumoto, A. E. Asato, M. Denny, Y. Shichida, T. Yashizawa and F. W. Dalquist, *J. Am. Chem. Soc.*, 1986, **103**, 7195.

2 Y.-Z. Huang, Y.-C. Shen, W.-Y. Ding, J.-H. Zheng, *Tetrahedron Lett.*, 1981, **22**, 5283; Y.-C. Shen, Y.-K. Lin and Y.-K. Xin, *Tetrahedron Lett.*, 1985, **26**, 5173; Y.-C. Shen and J.-H. Zheng, *J. Fluorine Chem.*, 1987, **35**, 513 and references cited therein.

3 Y.-C. Shen and T.-L. Wang, *Tetrahedron Lett.*, 1989, **30**, 7203.

4 S. Fiji, Y. Make and H. Kimoto, *J. Fluorine Chem.*, 1986, **33**, 329.

Paper 0/04704J
Received 19*th October* 1990
Accepted 29*th October* 1990