CHINESE JOURNAL OF CHEMISTRY **2002**, *20*, 1375—1378

Reaction of Grignard Reagents with Diethyl Perfluoroacyl (1-Cyanoethyl) phosphonates. Synthesis of Perfluoroalkylated *α*, *β*-Unsaturated Nitriles with Predominant *Z*-Selectivity[†]

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Diethyl (1-cyanoethyl)phosphonate 1 was reacted with *n*-butyllithium in tetrahydrofuran (THF) at − 78 ℃ and the resulting carbanion 2 reacted with perfluoroalkanoic acid anhydride to afford perfluoroacylated phosphonate 3. Without isolation 3 was attacked by Grignard reagents giving perfluoroalkylated *α*, *β*-unsaturated nitriles in 46%—88% yields with high *Z*-stereoselectivity (*Z*: *E* = 89—62:11—38).

Keywords perfluoroalkylated *α*, *β*-unsaturated nitrile, Grignard reagent, diethyl (1-cyanoethyl)phosphonate, *Z*-selectivity

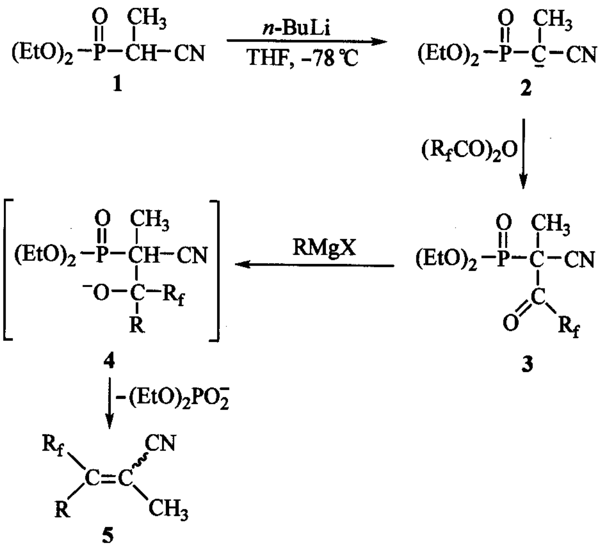
Introduction

Recently much attention has been devoted to the synthesis of *α*, *β*-unsaturated nitriles since they are important structural feature of several naturally occurring biologically active compounds.[1,2] The introduction of fluorine or trifluoromethyl group into biologically active compounds often gives rise to unique physiological activities,[3,4] and organofluorine compounds are increasingly being applied in pharmaceuticals, agrochemicals and other fields.[5-7] Such compounds and their fluoro species are capable of undergoing many organic transformation in organic synthesis,[8-10] and are employed as intermediates in the synthesis of biologically active compound.[11,12] A number of synthetic methods for their preparation have been reported.[13-15] However, the synthesis of title compounds are still limited. In our previous papers,[16,17] the synthesis of perfluoroalkylated *α*, *β*-unsaturated nitriles has been reported, but the *E*-isomer was obtained as the major product. We now wish to report the synthesis of perfluoroalkylated *α*, *β*-unsaturated nitriles with predominant *Z*-selectivity by the reaction of Grignard reagents with diethyl perfluoroacyl (1-cyanoethyl)phosphonates.

Results and discussion

The reaction sequence is shown in Scheme 1.

Scheme 1



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Received April 17, 2002; revised June 6, 2002; accepted June 24, 2002.

Project supported by the National Natural Science Foundation of China (No. 29972046) and Chinese Academy of Sciences.

[†] Dedicated to Professor HUANG Yao-Zeng on the occasion of his 90th birthday.

The phosphonate anion **2**, generated from the diethyl (1-cyanoethyl) phosphonate and *n*-butyllithium in tetrahydrofuran (THF), was acylated by the addition of perfluoroalkanoic anhydride affording perfluoroacylated phosphonates **3**. Without isolation **3** was attacked by Grignard reagents, followed by elimination of phosphonic acid anion giving the desired products **5** in 46%—88% yields. The results are summarized in Table 1.

Table 1 Preparation of perfluoroalkylated α, β-unsaturated nitriles

Compound	R	R_f	Yield (%)[a]	Ratio $(Z:E)$[b]
5a	$C_6H_5C\equiv C$	CF_3	88	89:11
5b	4-$CH_3C_6H_4$	CF_3	55	85:15
5c	4-ClC_6H_4	CF_3	82	81:19
5d	$C_6H_5C\equiv C$	C_3F_7	57	80:20
5e	$C_6H_5C\equiv C$	C_2F_5	71	78:22
5f	$C_4H_9C\equiv C$	CF_3	69	77:23
5g	C_6H_5	CF_3	57	67:33
5h	C_6H_5	C_3F_7	46	62:38

[a] Isolated yields. [b] The ratio of E- to Z-isomers is estimated on the basis of NMR spectra.

When the trifluoromethyl group is *trans* with respect to the cyano group, the chemical shifts of the trifluoromethyl group appear upfield, while those *cis* with respect to the cyano group are shifted slightly downfield.[17] The same is true for a difluoro moiety adjacent to the double bond in the pentafluoroethyl or heptafluoropropyl group. Thus the relative proportions of Z- and E-isomers could be determined.

The difference of stereochemical results between Grignard and lithium reagents cannot be rationalized satisfactorily by using the concepts of the kinetic and thermodynamic control of the selectivity and the detailed mechanism is being pursued.

Experimental

Boiling points (the oven temperature) were uncorrected. IR spectra of products were obtained as films on a Digilab FTS-20E spectrometer. ^{19}F NMR spectra were recorded on a Varian EM-360 (60 MHz) spectrometer with TFA as external standard, positive for upfield shifts. ^1H NMR spectra were obtained on a Bruker AM-300 (300 MHz) instrument with TMS as reference and $CDCl_3$ was used as solvent, coupling constant (J) is in Hz. Mass spectra were measured on a Finnigan GC-MS-4021 mass spectrometer.

Diethyl (1-cyanoethyl) phosphonate **1** was prepared according to the known method.[18]

General procedure for the preparation of perfluoroalkylated α,β-unsaturated nitriles (**5**)

To a solution (15 mL absolute THF) of diethyl (1-cyanoethyl) phosphonate (**1**, 0.32 g, 2 mmol), butyllithium (2 mmol) was added at −78 ℃ under nitrogen giving the phosphoryl-stabilized carbanion (**2**). After the reaction mixture was stirred at −78 ℃ for 0.5 h under nitrogen, perfluoroalkanoic anhydride (2 mmol) was added to it in one portion. Stirring was continued at −78 ℃ for 0.5 h and the reaction mixture was allowed to warm to room temperature. Then Grignard reagent (3 mmol) was added dropwise to the mixture, which was stirred for further 2 h. The mixture was poured into aqueous 1 mol/L HCl solution (30 mL) and the water layer was extracted with diethyl ether (3×15 mL). The combined organic layer was washed with brine (3×10 mL) and water (3×10 mL) and dried over $MgSO_4$. Evaporation of the solvent gave a residue, which was purified by column chromatography eluting with petroleum ether (60—90 ℃)-ethyl acetate ($V:V$, 98:2) to give the product **5**.

5-Phenyl-3-trifluoromethyl-2-methyl-pent-2-en-4-ynenitrile (**5a**) Ratio $Z:E=89:11$, b.p. 95 ℃/1.3×10^2 Pa (Lit.[17b] $Z:E=45:55$, b.p. 92 ℃/1.3×10^2 Pa), ^1H NMR ($CDCl_3$) δ: 2.26 (q, $J=2.5$ Hz, $0.89\times 3H$, Z), 2.36 (q, $J=2.1$ Hz, $0.11\times 3H$, E), 7.35—7.59 (m, 5H); ^{19}F NMR ($CDCl_3$) δ: −17.3 (s, $0.89\times 3F$, Z), −15.1 (s, $0.11\times 3F$, E); IR (film) ν: 2200, 1600, 1360, 1260, 760, 690 cm^{-1}; MS (70 eV) m/z (%): 235 (M^+, 100), 215 (14), 166 (56), 140 (21), 115 (7).

4, 4, 4-Trifluoromethy-3-(4-methylphenyl)-2-methyl-but-2-enenitrile (**5b**) Ratio $Z:E=85:15$, b.p. 90 ℃/1.3×10^2 Pa, ^1H NMR ($CDCl_3$) δ: 1.95 (q, $J=2.1$ Hz, $0.15\times 3H$, E), 2.30 (q, $J=2.7$ Hz, $0.85\times 3H$, Z), 2.40 (s, 3H), 7.08—7.28 (m, 4H); ^{19}F NMR ($CDCl_3$) δ: −18.8 (s, $0.85\times 3F$, Z), −14.3 (s, $0.15\times 3F$, E); IR (film) ν: 2230, 1610, 1510, 1340, 1200, 820 cm^{-1}; MS (70 eV) m/z (%): 225 (M^+, 100), 156 (38), 140 (16), 129 (30). Anal. calcd for $C_{12}H_{10}F_3N$ (225.21): C 64.00, H 4.48, N 6.22; found C 64.07, H 4.56, N 6.07.

4, 4, 4-*Trifluorometty-*3-(4-*chlorolphenyl*)-2-*methyl-but-*2-*enenitrile* (**5c**) Ratio $Z:E = 81:19$, b.p. 92 ℃/1.3×10^2 Pa, ^{1}H NMR ($CDCl_3$) δ: 1.94 (q, $J = 2.0$ Hz, $0.19\times3H$, E), 2.31 (q, $J = 2.6$ Hz, $0.81\times3H$, Z), 7.15 (d, $J = 8.4$ Hz, $0.19\times2H$, E), 7.28 (d, $J = 8.5$ Hz, $0.81\times2H$, Z), 7.42—7.47 (m, 2H); ^{19}F NMR ($CDCl_3$) δ: -19.0 (s, $0.81\times3F$, Z), -15.5 (s, $0.19\times3F$, E); IR (film) ν: 2230, 1640, 1590, 1490, 1230, 1200, 940, 830 cm^{-1}; MS (70 eV) m/z (%): 247 ($M^+ + 2$, 38), 245 (M^+, 100), 210 (33), 190 (65), 140 (28). Anal. calcd for $C_{11}H_7ClF_3N$ (245.63): C 53.79, H 2.87, N 5.70; found C 53.56, H 2.98, N 5.76.

6, 6, 6, 5, 5, 4, 4-*Heptafluoro-*3-*phenylacetyl-*2-*methyl-hex-*2-*enenitrile* (**5d**) Ratio $Z:E = 80:20$, b.p. 112 ℃/1.3×10^2 Pa, ^{1}H NMR ($CDCl_3$) δ: 2.27 (t, $J = 2.8$ Hz, $0.80\times3H$, Z), 2.42 (t, $J = 2.0$ Hz, $0.20\times3H$, E), 7.37—7.57 (m, 5H); ^{19}F NMR ($CDCl_3$) δ: 2.8 (s, $0.80\times3F$, Z), 3.6 (s, $0.20\times3F$, E), 30.2 (m, $0.80\times2F$, Z), 31.5 (m, $0.20\times2F$, E), 48.1 (s, $0.20\times2F$, E), 48.6 (s, $0.80\times2F$, Z); IR(film) ν: 2200, 1600, 1560, 1360, 1240, 760, 690 cm^{-1}; MS (70 eV) m/z (%): 335 (M^+, 100), 216 (69), 166 (44), 140 (31), 91 (48), 77 (24), 44 (60). Anal. calcd for $C_{15}H_8F_7N$ (335.22): C 53.74, H 2.41, N 4.18; found C 53.45, H 2.26, N 4.14.

5, 5, 5, 4, 4-*Pentafluoro-*3-*phenylacetyl-*2-*methyl-pent-*2-*enenitrile* (**5e**) Ratio $Z:E = 78:22$, b.p. 98 ℃/1.3×10^2 Pa (Lit.[17b] $Z:E = 20:80$, b.p. 94 ℃/1.3×10^2 Pa), ^{1}H NMR ($CDCl_3$) δ: 2.27 (t, $J = 3.1$ Hz, $0.78\times3H$, Z), 2.42 (t, $J = 2.0$ Hz, $0.22\times3H$, E), 7.35—7.58 (m, 5H); ^{19}F NMR ($CDCl_3$) δ: 6.0 (s, 3F), 33.3 (s, $0.78\times3F$, Z), 34.7 (s, $0.22\times3F$, E); IR (film) ν: 3060, 2200, 1590, 1330, 1210, 750, 690 cm^{-1}; MS (70 eV) m/z (%): 285 (M^+, 100), 216 (47), 166 (48), 140 (28), 69 (47).

3-*Trifluoromethyl-*2-*methyl-non-*2-*en-*4-*ynenitrile* (**5f**) Ratio $Z:E = 77:23$, b.p. 80 ℃/1.3×10^2 Pa (Lit.[17b] $Z:E = 57:43$, b.p. 76 ℃/1.3×10^2 Pa), ^{1}H NMR ($CDCl_3$) δ: 0.88—0.95 (m, 3H), 1.29—1.64 (m, 4H), 2.17 (q, $J = 2.4$ Hz, $0.77\times3H$, Z), 2.24 (q, $J = 1.8$ Hz, $0.23\times3H$, E), 2.43—2.50 (m, 2H); ^{19}F NMR ($CDCl_3$) δ: -17.2 (s, $0.77\times3F$, Z), -14.6 (s, $0.23\times3F$, E); IR (film) ν: 2940, 2210, 1600, 1460, 1230, 1150 cm^{-1}; MS (70 eV) m/z (%): 216 ($M^+ + 1$, 100), 200 (92), 160 (53), 146 (49).

4, 4, 4-*Trifluoro-*3-*phenyl-*2-*methyl-but-*2-*enenitrile* (**5g**) Ratio $Z:E = 67:33$, b.p. 85 ℃/1.3×10^2 Pa (Lit.[17b] $Z:E = 25:75$, b.p. 92 ℃/1.3×10^2 Pa), ^{1}H NMR ($CDCl_3$) δ: 1.94 (q, $J = 2.0$ Hz, $0.33\times3H$, E), 2.32 (q, $J = 2.4$ Hz, $0.67\times3H$, Z), 7.19—7.22 (m, $0.33\times2H$), 7.32—7.37 (m, $0.67\times2H$), 7.44—7.48 (m, 3H); ^{19}F NMR ($CDCl_3$) δ: -19.3 (s, $0.67\times3F$, Z), -15.7 (s, $0.33\times3F$, E); IR (film) ν: 2220, 1630, 1340, 1230, 770, 700 cm^{-1}; MS (70 eV) m/z (%): 211 (M^+, 100), 184 (25), 142 (30), 115 (62).

6, 6, 6, 5, 5, 4, 4-*Heptafluoro-*3-*phenyl-*2-*methy-hex-*2-*enenitrile* (**5h**) Ratio $Z:E = 62:38$, b.p. 101 ℃/1.3×10^2 Pa, ^{1}H NMR ($CDCl_3$) δ: 1.94 (t, $J = 2.4$ Hz, $0.38\times3H$, E), 2.31 (t, $J = 3.2$ Hz, $0.62\times3H$, Z), 7.16—7.55 (m, 5H); ^{19}F NMR ($CDCl_3$) δ: 3.0 (s,3F), 29.0 (m, $0.62\times2F$, Z), 30.5 (m, $0.38\times2F$, E), 46.4 (s, $0.38\times2F$, E), 47.1 (s, $0.62\times2F$, Z); IR (film) ν: 3060, 2230, 1620, 1400, 1220, 850, 760 cm^{-1}; MS (70 eV) m/z (%): 311 (M^+, 100), 19 2(60), 165 (23), 142 (20), 115 (31). Anal. calcd for $C_{13}H_8F_7N$ (311.20): C 50.17, H 2.59, N 4.50; found C 49.90, H 2.56, N 4.28.

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(E0204172 LU, Y. J.; ZHENG, G. C.)