Available online at www.sciencedirect.com
SCIENCE DIRECT®
Journal of Fluorine Chemistry 124 (2003) 65–68
JOURNAL OF FLUORINE CHEMISTRY
www.elsevier.com/locate/jfluchem

Stereoselective synthesis of (*Z*)-γ-cyano-β-perfluoroalkyl-β,γ-unsaturated esters

Yanchang Shen*, Jiahong Ni

State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, PR China

Received 5 March 2003; received in revised form 24 June 2003; accepted 26 June 2003

Abstract

(*Z*)-γ-Cyano-β-perfluoroalkyl-β,γ-unsaturated esters have been synthesized by the reaction of perfluoroacylated phosphonates with organozinc reagent in 50–71% (three steps) yields.

Keywords: γ-Cyano-β-perfluoroalkyl-β,γ-unsaturated ester; β,γ-Unsaturated ester; Perfluoroacylated phosphonates; Stereoselective synthesis

1. Introduction

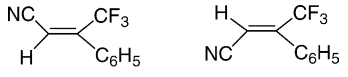
β,γ-Unsaturated acids and their esters are useful intermediates in organic synthesis and have been noted as important functional groups in naturally occurring compounds [1,2]. They also can undergo useful organic transformation converting to lactones, which are the important framework in natural products [3,4]. The well known Wittig and Horner–Wadsworth–Emmons (HWE) reactions have frequently been used for the synthesis of α,β-unsaturated acids and their esters with control of the geometry of the double bond [5–7]. β,γ-Unsaturated acids esters are generally less readily available substances than their α,β-unsaturated analogs since they are thermodynamically unstable regioisomers [8]. Recently, several methods including palladium-catalyzed carbonylation of allylic halides under two-phase conditions for the synthesis of β,γ-unsaturated acids esters have been reported [9,10]. However, examples of the synthesis of β,γ-unsaturated esters by Wittig and HWE reactions are still limited [11], particularly for the synthesis of fluoro species [12,13]. Therefore to develop an effective method for their synthesis would be valuable.

2. Results and discussion

In our continuing investigation of the application of sequential transformation of phosphonates in organic synthesis [14–16], herein we report the stereoselective synthesis of (*Z*)-γ-cyano-β-perfluoroalkyl-β,γ-unsaturated esters via the sequential transformation of phosphonates in 50–71% (three steps) yields. The reaction sequence is shown in Scheme 1.

The phosphoryl-stabilized carbanion **2**, generated from the corresponding phosphonate and *n*-butyllithium in tetrahydrofuran (THF), was acylated by the addition of perfluoroalkanoic anhydride to afford perfluoroacylated phosphonate **3**. Without isolation **3** was attacked by organozinc reagent and elimination of phosphonic acid anion gave (*Z*)-γ-cyano-β-perfluoroalkyl-β,γ-unsaturated esters **4**. The results are summarized in Table 1.

On the basis of data reported in the literature [17a], if the trifluoromethyl group is *cis* with respect to the cyano group (*Z*-isomer), the chemical shift of the trifluoromethyl group is −15.6 ppm, while that *trans* with respect to the cyano group (*E*-isomer) is −10.9 ppm.



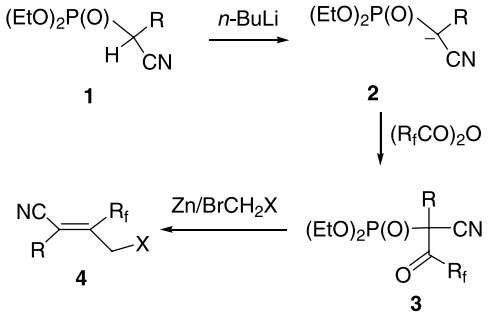
Z-isomer δ_{CF_3} = -15.6 ppm

E-isomer δ_{CF_3} = -10.9 ppm

This compound is similar with compounds **4**, therefore, we assign **4** with the chemical shifts of CF_3 in the range of −16.2 to −17.8 ppm as the *Z*-isomer. The same is true for the difluoro moiety adjacent to the double bond in pentafluoroethyl or heptafluoropropyl group [17b]. In the cases of **4g** and **4h** only one isomer was obtained exclusively no other isomer was isolated or detectable. Thus, according to the

* Corresponding author. Tel.: +86-21-64163300; fax: +86-21-64166128.
E-mail address: shenyc@mail.sioc.ac.cn (Y. Shen).

0022-1139/$ – see front matter © 2003 Elsevier B.V. All rights reserved.
doi:10.1016/S0022-1139(03)00175-1



Scheme 1.

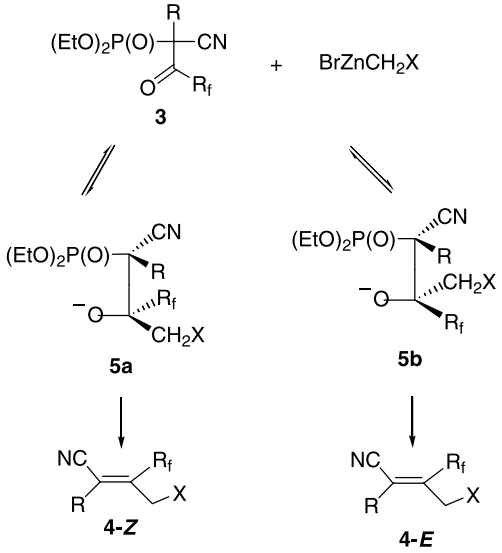
Table 1
(*Z*)-γ-Cyano-β-perfluoroalkyl-β,γ-unsaturated esters

Compound	R	X	R_f	Yield(%)[a]	*Z*:*E*[b]
4a	CH_3	CO_2Me	CF_3	71	100:0
4b	CH_3	CO_2Et	CF_3	68	100:0
4c	CH_3	CO_2Pr-*i*	CF_3	71	100:0
4d	CH_3	CO_2Bu-*t*	CF_3	66	100:0
4e	CH_2=$CHCH_2$	CO_2Et	CF_3	54	100:0
4f	CH_2=$CHCH_2$	CO_2Bu-*t*	CF_3	56	100:0
4g	CH_3	CO_2Et	C_2F_5	50	100:0
4h	CH_3	CO_2Et	C_3F_7	57	100:0

[a] Isolated yields.
[b] The ratios of *E*- and *Z*-isomers are estimated on the basis of NMR data.

mechanism (see later) for the formation of perfluoroalkyl-β,γ-unsaturated esters, the configuration of **4g** and **4h** could be ascertained as *Z*-isomers.

The stereoselectivity may be rationalized as shown in Scheme 2. The mechanism for the formation of perfluoroalkyl-β,γ-unsaturated esters is analogues to that of the bisphosphonates reported in the literature [18]. The reaction is initiated by nucleuophilic attack of organozinc reagents on



Scheme 2.

the carbon-oxygen double bond of the carbonyl group, forming two diasteroisomeric betaines **5a** and **5b** in equilibrium.

The size of reactive groups is $R_f > R$ (R: CH_3, CH_2=$CHCH_2$) > CH_2X > CN.[1] Since the intermediate **5a** involves an eclipsed orientation of two pairs of 'small/large' substituents (CN/R_f, CH_2X/R), this conformer should be favorable relative to the stereoisomer **5b**, which contains unfavorable 'large/large' (R_f/R) non-bonding interactions. Therefore, the stereoselectivity of olefination in our cases is a function of the conformational equilibrium of the adducts. Each of these intermediates decomposes via a *syn*-elimination, affording alkenes *Z*-**5** or *E*-**5**. In our case, formation of isomer **5a** will be favored over isomer **5b** and the *Z*-isomer was obtained exclusively.

In summary this methodology provides a convenient synthesis of (*Z*)-γ-cyano-β-perfluoroalkyl-β,γ-unsaturated esters, which would be useful intermediates in the synthesis of fluorine-containing biological active compounds.

3. Experimental

All boiling points are uncorrected. The IR spectra of liquid products were obtained as films on a Digilab FTS-20E spectrometer. ^{1}H NMR spectra were recorded on a Bruker AM-300 (300 MHz) spectrometer (δ values in ppm from tetramethylsilane, in $CDCl_3$, *J*-values are given in Hz). ^{19}F NMR spectra were taken on a Varian EM-360 (60 MHz) spectrometer (δ in ppm from external trifluoroacetic acid, in $CDCl_3$, positive for upfield shifts). Mass spectra were measured on a Finnigan GC–MS-4021 mass spectrometer. High resolution mass spectrometry data were obtained on a Finnigan-Mat 8430 high-resolution mass spectrometer. Diethyl(1-cyanoethyl)phosphonate was purchased from Aldrich Company. Diethyl(1-cyanobut-3-enyl)phosphonate was prepared according to the known method [20].

3.1. General procedure for the preparation of γ-cyano-β-perfluoroalkyl-β,γ-unsaturated esters

Treatment of phosphonate **1** with *n*-butyllithium (3 mmol) at −78 °C in absolute THF (15 ml) gave the phosphoryl-stabilized carbanion **2**, which was stirred at −78 °C for 0.5 h under nitrogen. Perfluoroalkanoic anhydride (3 mmol) was added to it in one portion. After stirring at −78 °C for 1 h, the reaction mixture was allowed to warm to 25 °C and the organozinc reagent (3 mmol, prepared from 3 mmol of bromoacetic ester and 9 mmol (0.58 g) zinc powder) was added. The mixture was stirred for further 4 h and poured into water (30 ml). The water layer was extracted with diethyl ether (3 ml × 15 ml). The combined organic layer

[1] It has been reported in this paper that space-filling models indicate that the steric hindrance between the CH_3 group and the CO_2CH_3 group is larger than that between $CH_2PO(OEt)_2$ group and the CO_2CH_3 group [19].

was washed with water (3 ml × 10 ml) and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by column chromatography eluting with petroleum ether (60–90 °C)-ethyl acetate (98:2) to give the product **4**.

*3.1.1. Z-Methyl 4-cyano-3-trifluoromethylpent-3-enoate (**Z-4a**)*

Yield: 71%; bp = 72 °C/2 mmHg; *Z*:*E* = 100:0. IR (film) (cm^{-1}): 2960, 2230, 1750, 1650, 1350, 1230, 1140, 1040. ^{1}H NMR ($CDCl_3$/TMS): δ 2.22(q, J = 1.3 Hz, 3H), 3.61(s, 2H), 3.77(s 3H). ^{19}F NMR ($CDCl_3$/TFA): δ −16.2(s, 3F). MS *m*/*z* (rel. int.): 207(M^+, 1), 206(2), 187(20), 176(19), 163(34), 162(29), 148(100). 128(57). Anal. Calcd. for $C_8H_8F_3NO_2$ (207.15): C, 46.39; H, 3.89; N, 6.76. Found: C, 46.44; H, 3.86; N, 7.13%.

*3.1.2. Z-Ethyl 4-cyano-3-trifluoromethylpent-3-enoate (**Z-4b**)*

Yield: 68%; bp = 76 °C/2 mmHg; *Z*:*E* = 100:0. IR (film) (cm^{-1}): 2990, 2230, 1750, 1650, 1350, 1230, 1140, 1040. ^{1}H NMR ($CDCl_3$/TMS): δ 1.29(t, J = 7.1 Hz, 3H), 2.21(q, J = 1.7 Hz, 3H), 3.59(s, 2H), 4.22(q, J = 7.1 Hz, 2H). ^{19}F NMR ($CDCl_3$/TFA): δ −16.9(s, 3F). MS *m*/*z* (rel. int.): 222($M^+ + 1$, 11), 194(6), 176(41), 149(100), 148(74), 128(31). HRMS: *m*/*z* calcd. for $C_9H_{10}F_3NO_2$, 221.0664; found, 221.0688.

*3.1.3. Isopropyl 4-cyano-3-trifluoromethylpent-3-enoate (**Z-4c**)*

Yield: 71%; bp = 80 °C/2 mmHg; *Z*:*E* = 100:0. IR (film) (cm^{-1}): 2990, 2230, 1740, 1650, 1340, 1230, 1140, 1100. ^{1}H NMR ($CDCl_3$/TMS): δ 1.25(d, J = 6.4 Hz, 6H), 2.19(q, J = 1.4 Hz, 3H), 3.54(s, 2H), 5.05(sept, J = 6.4 Hz, 1H). ^{19}F NMR ($CDCl_3$/TFA): δ −16.9(s, 3F). MS *m*/*z* (rel. int.): 220($M^+ - 15$, 1), 176(26), 149(27), 148(64), 128(18), 101(7), 43(100). Anal. Calcd. for $C_{10}H_{12}F_3NO_2$ (235.20): C, 51.07; H, 5.14; N, 5.96. Found: C, 50.91; H, 4.96; N, 6.10%.

*3.1.4. Z-t-Butyl 4-cyano-3-trifluoromethylpent-3-enoate (**Z-4d**)*

Yield: 66%; bp = 76 °C/2 mmHg; *Z*:*E* = 100:0. IR (film) (cm^{-1}): 2990, 2230, 1740, 1660, 1340, 1160, 1040. ^{1}H NMR ($CDCl_3$/TMS): δ 1.47(s, 9H), 2.20(q, J = 1.3 Hz, 3H), 3.52(s, 2H). ^{19}F NMR ($CDCl_3$/TFA): δ −16.7(s, 3F). MS *m*/*z* (rel. int.): 250($M^+ + 1$, 7), 234(2), 194(7), 176(5), 148(21), 128(11), 57(100). HRMS: *m*/*z* calcd. for $C_{11}H_{14}F_3NO_2$, 249.0977; found, 249.0976.

*3.1.5. Z-Ethyl 4-cyano-3-trifluoromethylhept-3,6-dienoate (**Z-4e**)*

Yield: 54%; bp = 84 °C/2 mmHg; *Z*:*E* = 100:0. IR (film) (cm^{-1}): 2990, 2230, 1750, 1640, 1340, 1260, 1190. ^{1}H NMR ($CDCl_3$/TMS): δ 1.29(t, J = 7.1 Hz, 3H), 3.24(d, J = 6.1 Hz, 2H), 3.61(s, 2H), 4.22(q, J = 7.1 Hz, 2H), 5.29(d, J = 10.1 Hz, 1H), 5.30(d, J = 16.6 Hz, 1H), 5.74–5.90(m, 1H). ^{19}F NMR ($CDCl_3$/TFA): δ −17.8(s, 3F). MS *m*/*z* (rel. int.): 248($M^+ + 1$, 18), 247(M^+, 5), 202(97), 175(75), 174(100), 154(41), 127(54), 106(98). Anal. Calcd. for $C_{11}H_{12}F_3NO_2$ (247.21): C, 53.44; H, 4.89; N, 5.67. Found: C, 53.20; H, 4.72; N, 5.78%.

*3.1.6. Z-t-Butyl 4-cyano-3-trifluoromethylhept-3,6-dienoate (**Z-4f**)*

Yield: 56%; bp = 84 °C/2 mmHg; *Z*:*E* = 100:0. IR (film) (cm^{-1}): 2980, 2230, 1740, 1640, 1340, 1260, 1140. ^{1}H NMR ($CDCl_3$/TMS): δ 1.47(s, 9H), 3.22(d, J = 6.3 Hz, 2H), 3.53(s, 2H), 5.28(d, J = 10.3 Hz, 1H), 5.29(d, J = 17.7 Hz, 1H), 5.74–5.90(m, 1H). ^{19}F NMR ($CDCl_3$/TFA): δ −17.8(s, 3F). MS *m*/*z* (rel. int.): 276($M^+ + 1$, 1), 260(3), 202(8), 174(6), 154(5), 127(8), 57(100). HRMS: *m*/*z* calcd. for $C_{13}H_{16}F_3NO_2$, 275.1133; found, 275.1103.

*3.1.7. Z-Ethyl 4-cyano-3-pentafluoroethylpent-3-enoate (**Z-4g**)*

Yield: 50%; bp = 68 °C/2 mmHg; *Z*:*E* = 100:0. IR (film) (cm^{-1}): 2990, 2230, 1750, 1660, 1330, 1210, 1190. ^{1}H NMR ($CDCl_3$/TMS): δ 1.29(t, J = 7.1 Hz, 3H), 2.30(br.s, 3H), 3.54(s, 2H), 4.23(q, J = 7.1 Hz, 2H). ^{19}F NMR ($CDCl_3$/TFA): δ 5.1(s, 3F), 34.9(s, 2F). MS *m*/*z* (rel. int.): 272($M^+ + 1$, 1), 226(20), 199(100), 198(66), 128(16). HRMS: *m*/*z* calcd. for $C_{10}H_{10}F_5NO_2$, 271.0632; found, 271.0656.

*3.1.8. Z-Ethyl 4-cyano-3-heptafluoropropylpent-3-enoate (**Z-4h**)*

Yield: 57%; bp = 76 °C/2 mmHg; *Z*:*E* = 100:0. IR (film) (cm^{-1}): 2990, 2230, 1750, 1650, 1350, 1240, 1190. ^{1}H NMR ($CDCl_3$/TMS): δ 1.29(t, J = 7.1 Hz, 3H), 2.23(br.s, 3H), 3.54(s, 2H), 4.23(q, J = 7.1 Hz, 2H). ^{19}F NMR ($CDCl_3$/TFA): δ 2.9(t, J = 10 Hz, 3F), 32.4(q, J = 10 Hz, 2F), 44.8(s, 2F). MS *m*/*z* (rel. int.): 322($M^+ + 1$, 8), 276(26), 249(100), 228(12), 199(11). HRMS: *m*/*z* calcd. for $C_{11}H_{10}F_7NO_2$, 321.0600; found, 321.0607.

Acknowledgements

The authors thank the National Natural Science Foundation of China and Chinese Academy of Sciences for financial support.

References

[1] T. Hirao, Y. Fujihara, K. Kurokawa, Y. Ohshiro, T. Agawa, J. Org. Chem. 51 (1986) 2830–2832, and references cited therein.
[2] M. Deng, N. Li, Y. Huang, J. Org. Chem. 58 (1993) 1949–1951.
[3] O. Piva, Tetrahedron 50 (1994) 13687–13696.
[4] A. Kayano, Y. Yajima, M. Akazome, M. Fujita, K. Ogura, Bull. Chem. Soc. Jpn. 68 (1995) 3599–3609.
[5] B.E. Maryanoff, A.B. Reitz, Chem Rev. 89 (1989) 836–927.

[6] D.J. Burton, Z.Y. Yang, W. Qiu, Chem. Rev. 96 (1996) 1641–1715.
[7] Y. Shen, Acc. Chem. Res. 31 (1998) 584–592.
[8] G. Cardillo, A. De Simone, A. Mingardi, C. Tomasini, Synlett. (1995) 1131–1132.
[9] J. Kiji, T. Okano, Y. Higashimae, Y. Fukui, Bull. Chem. Soc. Jpn. 69 (1996) 1029–1031.
[10] J. Szymoniak, S. Pagneux, D. Felix, C. Moise, Synlett. (1996) 46–48.
[11] A.R. Katritzky, D. Feng, H. Lang, J. Org. Chem. 62 (1997) 4131–4136.
[12] Y. Shen, Y. Xiang, J. Fluorine Chem. 51 (1991) 349–355.
[13] O. Piva, Synlett. (1994) 729–731.
[14] Y. Shen, J. Ni, J. Org. Chem. 62 (1997) 7260–7262.
[15] Y. Shen, P. Li, J. Sun, J. Org. Chem. 63 (1998) 9396–9398.
[16] Y. Shen, J. Ni, P. Li, J. Sun, J. Chem. Soc., Perkin Trans. I (1999) 509–512.
[17] (a) Y. Shen, S. Gao, J. Chem. Soc., Perkin Trans. I (1994) 1473–1475.;
(b) Y. Shen, J. Ni, J. Fluorine Chem. 86 (1997) 173–176.
[18] W. Perlikowska, M.J. Mphahlele, T.A. Modro, J. Chem. Soc., Perkin Trans. II (1997) 967–970.
[19] R.N. Gedye, K.C. Westaway, P. Arora, R. Bisson, A.H. Khalil, Can. J. Chem. 55 (1977) 1218–1228.
[20] A.A. Kandil, T.M. Porter, K.N. Slessor, Synthesis (1987) 411–413.