Highly stereoselective synthesis of tetrasubstituted perfluoroalkylated (Z)-α,β-unsaturated esters

Yanchang Shen *, Jiahong Ni

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

Abstract

Highly stereoselective synthesis of tetrasubstituted perfluoroalkylated (Z)-α,β-unsaturated esters by sequential transformations of phosphonates via three steps including deprotonation, perfluoroacylation and nucleophilic addition is described.   © 1998 Elsevier Science S.A. All rights reserved.

1. Introduction

Synthesis of α,β-unsaturated esters is attracting much attention, since such compounds are important structural features of a number of naturally occurring compounds which show biological activities [1–4] as exemplified in insect Juvenile hormone [5], alkaloids [6] and iridoid glucoside esters [7]. They are capable of undergoing many useful synthetic transformations and are utilized as essential compounds in synthesis of some natural products [8–12]. Change of physiological activity is often ascribed as the result of the introduction of fluorine atoms or perfluoroalkyl groups [13–15] and fluorinated α,β-unsaturated esters are attracting much interest in recent years, particularly for the synthesis of fluorine-containing biologically active compounds [16–20]. Recently, it has been of great interest to obtain α,β-unsaturated ester stereoselectively [21] and highly stereoselective syntheses of Z-unsaturated esters by using new Horner–Emmons reagents, ethyl (diarylphosphono)acetates have been reported [22]. However, to the best of our knowledge, no report has appeared in the literature concerning the preparation of tetrasubstituted perfluoroalkylated α,β-unsaturated esters except our previous paper [23] in which the E-isomers were obtained as the major products.

2. Results and discussion

Herein, we report a novel stereoselective synthesis of tetrasubstituted perfluoroalkylated (Z)-α,β-unsaturated esters by

* Corresponding author.
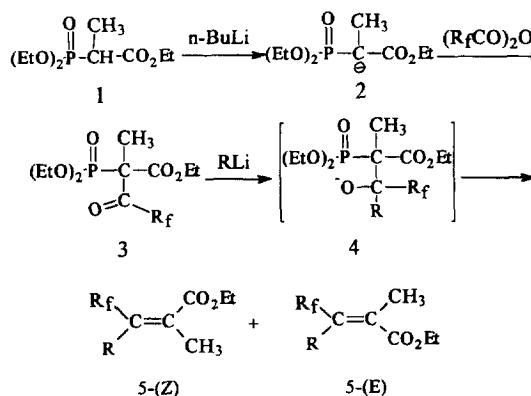
Scheme 1.

sequential transformations of phosphonates. We found that use of phosphonates is better than of phosphonium salts [23] since the starting materials are commercially available, cheap and the simplicity of isolation procedures would make this methodology practical in pharmaceutical and agrochemical industries. Furthermore, this methodology gave the (Z)-stereoselectivity.

The reaction sequence is shown in Scheme 1.

Treatment of diethyl (1-carbethoxy)ethylphosphonate 1 with n-butyllithium gave the phosphoryl-stabilized carbanion 2 which was acylated by the addition of perfluoroalkanoic anhydride affording perfluoroacylated phosphonates 3. Without isolation 3 were attacked regiospecifically by organolithium reagents, followed by elimination of phosphonic acid anion to give the products 5. The results are summarized in Table 1.

Table 1
Preparation of perfluoroalkylated α-methyl-α,β-unsaturated esters

Compound	R	R_f	Yield (%)[a]	$Z:E$[b]
5a	n-Bu	CF_3	62	99:1
5b	Ph	CF_3	57	99:1
5c	2-furyl	CF_3	52	99:1
5d	2-thienyl	CF_3	67	2:98[c]
5e	PhC≡C	C_2F_5	78	96:4
5f	PhC≡C	C_3F_7	66	92:8
5g	BuC≡C	CF_3	84	91:9
5h	BuC≡C	C_2F_5	75	90:10
5i	PhC≡C	CF_3	90	88:12
5j	BuC≡C	C_3F_7	68	80:20

[a] Isolated yields.
[b] The ratios of E- and Z-isomers were estimated on the basis of NMR data.
[c] According to sequence rules, when the perfluoroalkyl group is cis with respect to the ester group, the stereoisomer is assigned as the E-isomer and, conversely, it is assigned as Z-isomer in other cases.

Table 2
The effect of base on the yields and stereoselectivity of 5g

Entry	Base	Yield (%)[a]	$Z:E$[b]
1	BuLi	84	91:9
2	LDA	22	83:17
3	KOC_4H_9-t	15	81:19
4	$LiN(TMS)_2$	28	80:20
5	NaH	70	80:20

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

On the basis of data reported in the literature [24], the trifluoromethyl group is *trans* with respect to the CO_2R group (i.e., for compound 5-E) when the ^{19}F chemical shifts of trifluoromethyl group are upfield; while for the corresponding *cis* compounds (i.e., compound 5-Z), the chemical shifts are downfield. Hence, the isomers were identified and the relative proportions of Z- and E-isomers could be ascertained.

Several factors govern the reaction, such as base, solvent as well as reaction temperature and these have been studied in more detail with diethyl (1-carbethoxy)ethylphosphonate and lithium butylacetylide as reactants.

From Table 2, it is clearly shown that the base plays an important role in stereoselectivity and yields of the reaction and the butyllithium is the best base. There is no reasonable explanation for the effect of base on the stereoselectivity of the products.

From Table 3, entries 1, 2, 3 and 4, it can be seen that the reaction can give moderate to good yields in various solvents except DMF which reacts with butyllithium leading to the failure of the reaction.

From Table 3, entries 1, 5, 6 and 7, it is obvious that the yields were decreased as the temperature was increased and

Table 3
The effects of solvent and temperature on the yields and stereoselectivity of 4g

Entry	Solvent	Temperature (°C)	Yield (%)[a]	$Z:E$[b]
1	THF	−78	84	91:9
2	Et_2O	−78	71	91:9
3	CH_2Cl_2	−78	56	92:8
4	DMF	−78	0	
5	THF	−30	74	91:9
6	THF	0	55	91:9
7	THF	20	51	91:9

[a] Isolated yields.
[b] The ratios of Z- and E-isomer were estimated on the basis of NMR spectra.
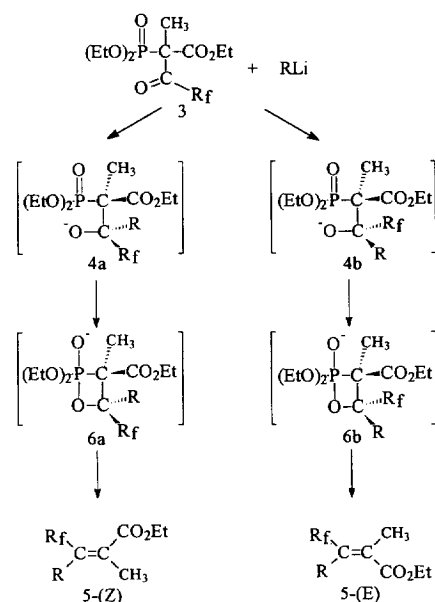
Scheme 2.

no change in stereoselectivity was observed as the temperature was increased.

The stereochemical results may be rationalized as follows (Scheme 2).

The reaction is initiated by nucleophilic attack on the carbon–oxygen double bond of the carbonyl group and for the additions containing asymmetric α-carbon, the Felkin–Anh model of asymmetric induction [25] predicts the predominant diastereomer. The incoming nucleophile preferentially attacks the less hindered side of the plane containing the C=O bond. The relative steric bulk of Me is smaller than that of CO_2Et, therefore the attack is from the rear (the side of plane containing the smaller group) of 3 forming the intermediate 4a; while the reverse is true for attack from the front forming intermediate 4b. Each of those intermediates decomposes via a syn elimination affording 5-(Z) or 5-(E). In our case, formation of 4a will be favored over 4b and the Z-isomer was obtained predominately (see Table 1).

3. Experimental

Bps are uncorrected. IR spectra of all products were obtained as film on a Perkin-Elmer 983 spectrometer. ^{19}F NMR spectra were recorded on a Varian EM-360 (60 M) spectrometer with CF_3CO_2H as external standard, positive for upfield shifts. ^{1}H NMR spectra were obtained on a Bruker AM-300 (300 M) instrument with $SiMe_4$ as reference; $CDCl_3$ was used as solvent; J-values are in hertz (Hz). Mass spectra were measured on a Finnigan GC-MS-4021 mass spectrometer. HRMS data were obtained on Finnigan-Mat 8430 high resolution mass spectrometer.

Lithium reagents: PhC≡CLi, BuC≡CLi, 2-furyllithium and 2-thienyllithium were prepared by reaction of corresponding terminal acetylenes, or furan or thiophene (3 mmol) with butyllithium (3 mmol) in tetrahydrofuran (THF) (10 ml) for 30 min at 0°C.

3.1. General procedure for the preparation of perfluoroalkylated α-methyl-α,β-unsaturated esters (5)

Treatment of diethyl (1-carbethoxy)ethylphosphonates **1** (3 mmol) with butyllithium (3 mmol) at −78°C in absolute THF (15 ml) gave the phosphoryl-stabilized carbanion which was stirred at −78°C for 0.5 h under nitrogen. Perfluoroalkanoic anhydride (3 mmol) was added in one portion. Stirring was continued at −78°C for 1 h after which the organolithium reagent (3 mmol) was added dropwise to the mixture which was stirred and allowed to warm to room temperature over 4 h. The reaction mixture was poured into water (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°C)–ethyl acetate (99:1) to give the product **5**.

3.2. Ethyl 3-(trifluoromethyl)-2-methyl-hept-2-enoate (5a)

Ratio $Z:E = 99:1$; b.p. 38°C 1 mm Hg^{-1}. HRMS m/z: 238.1197 (M^+), Calculated $C_{11}H_{17}F_3O_2 = 238.1181$. MS m/z (rel. Int): 239 ($M^+ + 1$,100); 193 (47); 161 (33); 43 (34). IR (film): 2980; 1730; 1660; 1467; 1270; 1190. ^{1}H NMR ($CDCl_3$) δ: 4.62 (q, 2H, $J = 7.1$); 2.25 (t, 2H, $J = 7.3$); 2.03 (q, 3H, $J = 2.1$); 1.53–1.42 (m, 2H); 1.42–1.25 (m, 2H); 1.35 (t, 3H, $J = 7.2$); 0.90 (t, 3H, $J = 7.1$) ppm. ^{19}F NMR ($CDCl_3$) δ: −17.7 (s, 0.99×3F, Z); (−14.7) (s, 0.01×3F, E) ppm.

3.3. Ethyl 4,4,4-trifluoro-3-phenyl-2-methyl-but-2-enoate (5b)

Ratio $Z:E = 99:1$; b.p.: 69°C 1 mm Hg^{-1} (Ref. [23], b.p. 80°C 2 mm Hg^{-1}). MS m/z (rel. Int): 258 (M^+, 100); 213 (98); 185 (40); 165 (71); 115 (99). IR (film): 1730; 1670; 1280; 1130. ^{1}H NMR ($CDCl_3$) δ: 7.45–7.15 (m, 5H); 3.85 (q, 2H, $J = 7.1$); 2.24 (q, 0.99×3H, $J = 2.5$, Z); 1.81 (q, 0.01×3H, $J = 2.1$, E); 0.82 (t, 3H, $J = 7.1$) ppm. ^{19}F NMR ($CDCl_3$) δ: −19.8 (s, 0.99×3F, Z); −16.4 (s, 0.01×3F, E) ppm.

3.4. Ethyl 4,4,4-trifluoro-3-(fur-2-yl)-2-methyl-but-2-enoate (5c)

Ratio $Z:E = 99:1$; b.p. 47°C 1 mm Hg^{-1}. HRMS m/z: 248.0626 (M^+), Calculated $C_{11}H_{11}F_3O_3 = 248.0660$. MS m/z (rel. Int): 248 (M^+, 74); 220 (100); 203 (74); 127 (86). IR (film): 1720; 1660; 1270; 1180. ^{1}H NMR ($CDCl_3$) δ: 7.41 (d, 1H, $J = 1.5$); 6.46 (brs, 1H); 6.41 (dd, 1H, $J = 3.3$, 1.7); 4.13 (q, 2H, $J = 7.1$); 2.24 (q, 0.99×3H, $J = 2.7$, Z); 2.13 (q, 0.01×3H, $J = 2.0$, E); 1.16 (t, 3H, $J = 7.1$) ppm. ^{19}F NMR ($CDCl_3$) δ: −19.2 (s, 0.99×3F, Z), −15.0 (s, 0.01×3F, E) ppm.

3.5. Ethyl 4,4,4-trifluoro-3-(thien-2-yl)-2-methyl-but-2-enoate (5d)

Ratio $Z:E = 2:98$; b.p. 55°C 1 mm Hg^{-1}. HRMS m/z: 264.0417 (M^+), Calculated $C_{11}H_{11}F_3O_2S = 264.0432$. MS m/z (rel. Int): 264 (M^+, 100); 219 (70); 191 (28); 121 (35). IR (film): 1730; 1650; 1280; 1160. ^{1}H NMR ($CDCl_3$) δ: 7.45–7.33 (m, 1H); 7.05–6.95 (m, 2H); 4.31 (q, 0.02×2H, $J = 7.1$, Z); 3.97 (q, 0.98×2H, $J = 7.1$, E); 2.24 (q, 0.98×3H, $J = 2.7$, E); 1.97 (q, 0.02×3H, $J = 2.1$, Z), 0.98 (t, 3H, $J = 7.1$) ppm. ^{19}F NMR ($CDCl_3$) δ: −18.3 (s, 0.98×3F, E), −15.4 (s, 0.02×3F, Z) ppm.

3.6. Ethyl 5-phenyl-3-(pentafluoroethyl)-2-methyl-pent-2-en-4-ynoate (5e)

Ratio $Z:E = 96:4$; b.p. 80°C 1 mm Hg^{-1}. HRMS m/z: 332.0786 (M^+), Calculated $C_{16}H_{13}F_5O_2 = 332.0836$. MS m/z (rel. Int): 332 (M^+, 100); 304 (40); 287 (47); 139 (46). IR (film): 2220; 1730; 1200. ^{1}H NMR ($CDCl_3$) δ: 7.46–7.38 (m, 2H); 7.36–7.28 (m, 3H); 4.33 (q, 2H, $J = 7.2$); 2.33 (t, 0.04×3H, $J = 2.0$, E); 2.22 (t, 0.96×3H, $J = 3.0$, Z); 1.34 (t, 3H, $J = 7.1$) ppm. ^{19}F NMR ($CDCl_3$) δ: 4.7 (s, 0.04×3F, E); 5.8 (s, 0.96×3F, Z); 32.1 (s, 0.96×2F, Z); 33.4 (s, 0.04×2F, E) ppm.

3.7. Ethyl 5-phenyl-3-(heptafluoropropyl)-2-methyl-pent-2-en-4-ynoate (5f)

Ratio $Z:E = 92:8$; b.p. 85°C 1 mm Hg^{-1}. HRMS m/z: 382.0798 (M^+), Calculated $C_{17}H_{13}F_7O_2 = 382.0804$. MS m/z (rel. Int): 382 (M^+, 100); 354 (36); 337 (44); 235 (64); 139 (83). IR (film): 2210; 1730; 1230; 1120. ^{1}H NMR ($CDCl_3$) δ: 7.46–7.36 (m, 2H); 7.36–7.30 (m, 3H); 4.35 (q, 2H, $J = 7.1$); 2.36 (t, 0.08×3H, $J = 2.0$, E); 2.23 (t, 0.92×3H, $J = 2.8$, Z); 1.35 (t, 3H, $J = 7.1$) ppm. ^{19}F NMR ($CDCl_3$) δ: 3.1 (t, 3F, $J = 10$); 29.5 (q, 0.92×2F, $J = 10$,

Z); 30.6 (q, 0.08×2F, $J=10$, E); 47.0 (s, 0.08×2F, E); 49.0 (s, 0.92×2F, Z) ppm.

3.8. Ethyl 3-(trifluoromethyl)-2-methyl-non-2-en-4-ynoate (5g)

Ratio $Z:E=91:9$; b.p. 53°C 1 mm Hg^{-1} (Ref. [23], b.p. 63°C 2 mm Hg^{-1}). MS m/z (rel. Int): 263 ($M^+ + 1$,100); 235 (55); 217 (44); 192 (47); 191 (35). IR (film): 2960; 2230; 1730; 1630; 1260; 1170. ^1H NMR (CDCl$_3$) δ: 4.27 (q, 2H, $J=7.1$); 2.35 (t, 2H, $J=6.6$); 2.15 (q, 0.09×3H, $J=2.5$, E); 2.12 (q, 0.91×3H, $J=1.8$, Z); 1.62–1.48 (m, 2H); 1.48–1.35 (m, 2H); 1.34 (t, 3H, $J=7.1$); 0.89 (t, 3H, $J=7.2$) ppm. ^{19}F NMR (CDCl$_3$) δ: -17.7 (s, 0.91×3F, Z); -15.5 (s, 0.09×3F, E) ppm.

3.9. Ethyl 3-(pentafluoroethyl)-2-methyl-non-2-en-4-ynoate (5h)

Ratio $Z:E=90:10$; b.p. 63°C 1 mm Hg^{-1}. Analysis: Calc. for $C_{14}H_{17}F_5O_2$ (312.28): C, 53.83; H, 5.49%. Found: C, 53.81; H, 5.43%. MS m/z (rel. Int): 313 ($M^+ + 1$,100); 285 (43); 267 (37); 242 (48). IR (film): 2980; 2230; 1730; 1210. ^1H NMR (CDCl$_3$) δ: 4.28 (q, 2H, $J=7.1$); 2.23 (t, 2H, $J=6.6$); 2.20 (t, 0.10×3H, $J=2.0$, E); 2.13 (t, 0.90×3H, $J=2.6$, Z); 1.55–1.45 (m, 2H); 1.45–1.35 (m, 2H); 1.34 (t, 3H, $J=7.1$); 0.90 (t, 3H, $J=7.1$) ppm. ^{19}F NMR (CDCl$_3$) δ: 5.0 (s, 0.10×3F, E); 6.0 (s, 0.90×3F, Z); 32.6 (s, 0.90×2F, Z); 34.0 (s, 0.10×2F, E) ppm.

3.10. Ethyl 5-phenyl-3-(trifluoromethyl)-2-methyl-pent-2-en-4-ynoate (5i)

Ratio $Z:E=88:12$; b.p. 75°C 1 mm Hg^{-1} (Ref. [23], b.p. 88°C 2 mm Hg^{-1}). MS m/z (rel. Int): 282 (M^+, 100); 237 (39); 209 (14); 197 (25); 139 (63). IR (film): 2210; 1730; 1630; 1230; 1140. ^1H NMR (CDCl$_3$) δ: 7.52–7.40 (m, 2H); 7.40–7.30 (m, 3H); 4.33 (q, 2H, $J=7.1$); 2.30 (q, 0.12×3H, $J=2.0$, E); 2.23 (q, 0.88×3H, $J=2.4$, Z); 1.35 (t, 3H, $J=7.1$) ppm. ^{19}F NMR (CDCl$_3$) δ: -18.1 (s, 0.88×3F, Z); -15.4 (s, 0.12×3F, E) ppm.

3.11. Ethyl 3-(heptafluoropropyl)-2-methyl-non-2-en-4-ynoate (5j)

Ratio $Z:E=80:20$; b.p. 69°C 1 mm Hg^{-1}. Analysis: Calc. for $C_{15}H_{17}F_7O_2$ (362.29): C, 49.71; H, 4.73%. Found: C, 49.30; H, 4.61%. MS m/z (rel. Int): 363 ($M^+ + 1$,100); 335 (29); 317 (33); 292 (28); 43 (21). IR (film): 2960; 2230;

1730; 1230; 1120. ^1H NMR (CDCl$_3$) δ: 4.29 (q, 0.8×2H, $J=7.1$, Z); 4.23 (q, 0.2×2H, $J=7.1$, E); 2.40 (t, 0.2×2H, $J=6.6$, E); 2.33 (t, 0.80×2H, $J=6.6$, Z); 2.21 (t, 0.20×3H, $J=2.1$, E); 2.11 (t, 0.80×3H, $J=2.7$, Z); 1.60–1.20 (m, 7H); 0.95–0.80 (m, 3H) ppm. ^{19}F NMR (CDCl$_3$) δ: 3.0 (t, 3F, $J=10$); 29.5 (q, 0.80×2F, $J=10$, Z); 31.0 (q, 0.20×2F, $J=10$, E); 47.8 (s, 0.20×2F, E); 49.0 (s, 0.80×2F, Z) ppm.

Acknowledgements

References

[1] A.R.H. Kehrli, D.A.H. Taylor, M. Niven, Phytochemistry 29 (1990) 153.

[2] R. Hernandez, A. Rivera, E. Suarez, J. Org. Chem. 54 (1989) 5343.

[3] M.H. Beale, Nat. Prod. Rep. 7 (1990) 25.

[4] T. Ikeda, S. Fugiwara, K. Araki, J. Kinjo, T. Nohara, T. Miyoshi, J. Nat. Prod. 60 (1997) 102.

[5] Y.C. Toong, D.A. Schooley, F.C. Baker, Nature (London) 333 (1988) 170.

[6] M.S. Al-Said, W.C. Evans, R.J. Grout, Phytochemistry 28 (1989) 3211.

[7] A.M. Dawidar, S.T. Esmirly, A.S.M. Al-Hajar, J. Jakupovic, M. Aldel-Mogib, Phytochemistry 28 (1989) 3227.

[8] P.D. Leeson, J. Chem. Soc. Perkin 1 (1984) 2125.

[9] J.P. Brennan, J.E. Saxton, Tetrahedron 42 (1986) 6719.

[10] D.M. David, G.W. O'Meara, S.G. Pyne, Tetrahedron Lett. 37 (1996) 5417.

[11] N. Ikota, Heterocycles 41 (1995) 983.

[12] Z.Y. Wei, E.E. Knaus, Org. Prep. Proc. Int. 26 (1994) 243.

[13] J.T. Welch, Tetrahedron 43 (1987) 3123.

[14] J.T. Welch, S. Eswarakrishmam, Fluorine in Biorganic Chemistry, Wiley, New York, 1991.

[15] G. Resnati, Tetrahedron 49 (1993) 9385.

[16] A.E. Asato, D. Mead, M. Denny, T.T. Bopp, R.S.H. Liu, J. Am. Chem. Soc. 104 (1982) 4979.

[17] F. Camps, R. Canela, J. Coll, A. Messeguer, A. Roca, Tetrahedron 34 (1978) 2179.

[18] W. Gartrer, D. Oesterhelt, P. Towner, J. Am. Chem. Soc. 103 (1981) 7642.

[19] D. Mead, A.E. Asato, M. Denny, R.S.H. Liu, Y. Hanzawa, T. Taguchi, A. Yamada, N. Kobayashi, A. Hosada, Y. Kobayashi, Tetrahedron Lett. 28 (1987) 259.

[20] A.E. Asato, R.S.H. Liu, Tetrahedron Lett. 27 (1986) 3337.

[21] M. Lanier, R. Pastor, J. Fluorine Chem. 75 (1995) 35.

[22] K. Ando, J. Org. Chem. 62 (1997) 1934.

[23] Y. Shen, Y. Xiang, J. Fluorine Chem. 52 (1991) 221.

[24] Y. Shen, S. Gao, J. Org. Chem. 58 (1993) 4564.

[25] E.P. Lodge, C.H. Heathcock, J. Am. Chem. Soc. 109 (1987) 3353.