Novel Conversion of *E* Stereoselectivity to *Z* Stereoselectivity in Trifluoromethylated α,β-Unsaturated Esters and Nitriles by way of *O*-Methylation of an Ylide Anion

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

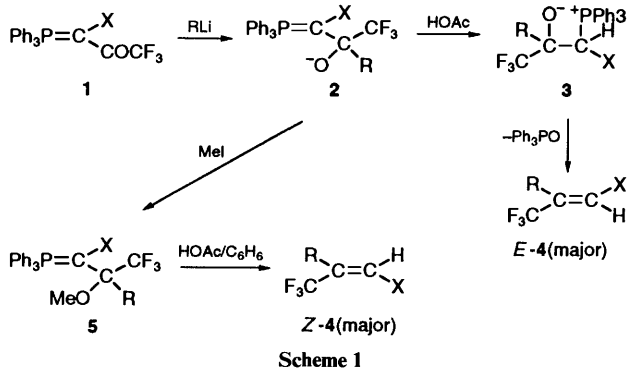
A stereocontrolled synthesis of (*Z*)-trifluoromethylated α,β-unsaturated esters and nitriles by way of *O*-methylation of an ylide anion is described.

Two important areas of research in which we are interested, namely the introduction of the CF_3 group into biologically active compound to increase their activity[1] and the control of stereochemistry in such systems,[2] are dealt with in the present study. Trifluoromethylated α,β-unsaturated esters, which are important intermediates for the synthesis of fluorine-containing organic compounds, have been prepared from trifluoromethyl ketones either by a Wittig condensation or a Horner–Emmons reaction to afford, predominantly, *E*-isomers.[3] The proportion of *Z*-isomer, the preparation of which has been reported to be rather cumbersome,[4] was enriched in an *E*/*Z* mixture by photosensitized isomerization of the double bond: at photoequilibrium the E:*Z* ratio was 57:43.[4] The two isomers were separated by a spinning distillation.[4]

Results and Discussion

Recently we found that trifluoromethylated α,β-unsaturated esters with *E*-isomers as major products could be conveniently synthesized by way of an intramolecular Wittig reaction[5] and fluorinated biscarbonyl phosphonium salt.[6] Similarly, *E*-isomers were obtained as major products in the preparation of perfluoroalkylated α,β-unsaturated nitriles.[7] Those methodologies gave, predominantly, *E*-isomers. We also found that fluorinated dicarbonyl triphenylphosphoranes could react with Grignard reagents to give β-oxido ylides. Treatment of β-oxido ylides with acetic acid or saturated methylamine hydrochloride gave *Z*-isomers as the major products; while 5% aqueous hydrochloric acid afforded predominantly *E*-isomer.[8] However, the β-oxido ylides generated from phenyl Grignard reagent only *E*-selectivity was observed.[8] We now report a novel conversion of *E*-selectivity to *Z*-selectivity by way of *O*-methylation of an ylide anion.

The reaction sequence is shown as follows:



Scheme 1

Reaction of fluorinated phosphoranes **1** with organolithium reagents gave the ylide anion **2** which, after protonation and elimination of triphenylphosphine oxide, afforded *E*-**4** as major product (method A). Before protonation the ylide anion **2** was allowed to react with methyl iodide to afford *O*-methylated products **5** which could be hydrolysed by acetic acid to give *Z*-**4** as a major product (method B). The *Z* and *E* isomers of **4a–c** could be separated conveniently by column chromatography on silica gel and those of **4d–g** could be separated by fractional distillation.[3b] The results are summarized in Table 1.

Since the intermediates **5** were stable enough to be isolated, their formation is established. These results are summarized in Table 2.

Experimental

Boiling (melting) points are uncorrected. IR spectra were recorded on a Shimadzu IR-440 spectrometer. ^{19}F NMR spectra were determined on a Varian EM-360 spectrometer (60M) with TFA as external standard; ^1H NMR spectra were carried out on a Varian EM-360 or a Bruke AM-300 (300M) instrument with TMS as reference; ^{31}P NMR spectra were obtained on a Bruker AM-300 instrument relative to 85% phosphoric acid as reference: $CDCl_3$ was used as solvent. Mass spectra were measured on a Finnigan GC–MS-4021 mass spectrometer. *J*-Values are in Hz.

General Procedure for the Preparation of Trifluoromethylated α,β-Unsaturated Esters and Nitriles **4a–g**.—*Method A.* Lithium reagent (4 mmol) was added dropwise with stirring to a solution of the ylide **1** (4 mmol) in dry THF (16 cm^3) at −60, −50 or 0 °C under nitrogen. The reaction mixture was stirred for 12 h at the same temperature to form the ylide anion **2**, after which acetic acid (1 cm^3) was added to it. The mixture was allowed to reach 20 °C after which it was stirred for 2 h and then diluted with diethyl ether (20 cm^3). The organic layer was separated, washed repeatedly with water to neutral pH, dried and evaporated. The residue was chromatographed on silica gel eluting with light petroleum (b.p. 60–90 °C)–ethyl acetate (97:3) to afford compound **4**.

Method B. The procedure was similar to that of method A. Before protonation, methyl iodide (5 mmol) was added to the reaction mixture which was then allowed to reach room temperature; it was then stirred overnight. Evaporation of the mixture gave a residue[8] to which acetic acid (1 cm^3) and benzene (20 cm^3) were added. The mixture was then refluxed for 1 h. Work-up was as described above.

Phenylacetylenyllithium was prepared by the reaction of acetylene (4 mmol) and phenyllithium (4 mmol) in THF (16 cm^3) at 0 °C for 1 h. Details are given in Table 1. Physical and spectral data are reported below.

4,4,4-Trifluoro-3-phenylbut-2-enenitrile **4a**.[7] *E*-Isomer, δ_H 7.56 (5 H, m) and 6.16 (1 H, s); δ_H −10.9 (s, 3 F); *Z*-isomer, δ_H 7.46 (5 H, m) and 5.90 (1 H, s); δ_F −15.6 (3 F, s).

5-Phenyl-3-trifluoromethylpent-2-en-4-ynenitrile **4b**.[7]

Table 1 Stereocontrolled synthesis of trifluoromethylated α,β-unsaturated esters and nitriles

Compound	R	X	T/°C[a]	Method[b]	$Z:E$[c]	Yield (%)[d]
4						
a	Ph	CN	−60	A	12:88	91[7]
a	Ph	CN	−60	B	87:13	93
b	PhC≡C	CN	0	A	8:92	98[7]
b	PhC≡C	CN	0	B	92:8	93
c	2-Thienyl	CN	0	A	0:100	90[7]
c	2-Thienyl	CN	0	B	88:12	94
d	Ph	CO_2Et	−50	A	8:92	95
d	Ph	CO_2Et	−50	B	62:38	85
e	2-Thienyl	CO_2Et	0	A	12:88	92
e	2-Thienyl	CO_2Et	0	B	87:13	93
f	Ph	CO_2Bu^t	−50	A	7:93	88
f	Ph	CO_2Bu^t	−50	B	84:16	87
g	2-Thienyl	CO_2Bu^t	0	A	12:88	92
g	2-Thienyl	CO_2Bu^t	0	B	70:30	85

[a] Reaction temperature of **1** with RLi. [b] Method A: ylide-anion was directly protonated; method B: ylide-anion was *O*-methylated and then protonated. [c] Isolated yields. All products were characterized by IR, NMR and mass spectroscopy. The new compounds also characterized by microanalysis. [d] The ratio of *Z*- and *E*-isomer was estimated on the basis of their NMR spectra.

Table 2 Isolation of some intermediates **5**[a]

Compound	R	X	Yield (%)[b]
a	Ph	CN	95
e	2-Thienyl	CO_2Et	85
f	Ph	CO_2Et	75

[a] All these compounds were characterized by IR, NMR, mass spectroscopy and microanalyses. [b] Isolated yields.

E-Isomer, δ_H 7.22 (5 H, m) and 5.93 (1 H, s); δ_F −9.2 (3 F, s); *Z*-isomer, δ_H 7.30 (5 H, m) and 5.78 (1 H, s); δ_F −12.7 (3 F, s).

4,4,4-*Trifluoro*-3-(2-*thienyl*)*but*-2-*enenitrile* **4c**. *E*-Isomer,[7] 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); *Z*-isomer, m.p. 37–38 °C; ν_{max}(film)/cm^{-1} 3100, 2210, 1610 and 730; δ_H 7.53 (1 H, d, *J* 5.0), 7.51–7.41 (1 H, m), 7.16 (1 H, dd, *J* 4.0 and 5.0) and 6.03 (1 H, s); δ_F −16.2 (3 F, s) (Found: C, 46.9; H, 2.0; N, 6.88. $C_8H_4F_3NS$ requires C, 47.29; H, 1.98; N, 6.89).

Ethyl 4,4,4-*trifluoro*-3-*phenylbut*-2-*enoate* **4d**.[8] Obtained as a mixture of *Z*- and *E*-isomers; δ_H 7.70–7.78 (5 H, m), 6.63 (q, *J* 1.3, *E*-isomer) and 6.36 (s, *Z*-isomer) (1 H), 4.34 and 3.97 (2 H, q, *J* 7.2, 1.38 and 1.07 (3 H, t, *J* 7.2); δ_F −10.0 (*Z*-isomer) and −17.3 (*Z*-isomer).

Ethyl 4,4,4-*trifluoro*-3-(2-*thienyl*)*but*-2-*enoate* **4e**. Obtained as a mixture of *Z*- and *E*-isomers, b.p. 90 °C/1.5 mmHg; ν_{max}/cm^{-1} 3100, 1730, 1640 and 710; *E*-isomer, δ_H 7.47 (1 H, dd, *J* 1.24 and 5.06), 7.24 (1 H, d, *J* 3.6), 7.08–7.05 (1 H, m), 6.59 (1 H, q, *J* 1.26), 4.16 (2 H, q, *J* 7.15) and 1.19 (3 H, t, *J* 7.15); δ_F −10.7 (3 F, s). *Z*-Isomer, δ_H 7.78–7.74 (1 H, m), 7.08–7.05 (2 H, m), 6.50 (1 H, s), 4.29 (2 H, d, *J* 7.18), 1.34 (3 H, t, *J* 7.18); δ_F −16.7 (3 F, s); *m*/*z* 250 (M^+, 1), 219 (3), 205 (4), 181 (1), 177 (3), 167 (3) and 43 (100) (Found: C, 47.79; H, 3.59. $C_{10}H_9F_3O_2S$ requires C, 47.99; H, 3.62).

tert-*Butyl* 4,4,4-*trifluoro*-3-*phenylbut*-2-*enoate* **4f**.[8] Obtained as a mixture of *Z*- and *E*-isomers; δ_H 7.44–7.20 (5 H, m), 6.49 (q, *J* 1.3, *E*-isomer) and 6.22 (s, *Z*-isomer) (1 H), 1.20 (9 H, s); δ_F −10.5 (*E*-isomer) and −17.3 (*Z*-isomer).

tert-*Butyl* 4,4,4-*trifluoro*-3-(2-*thienyl*)*but*-2-*enoate* **4g**. Obtained as a mixture of *Z*- and *E*-isomers, b.p. 95 °C/1.5 mmHg; ν_{max}(film)/cm^{-1} 3100, 2980, 1725, 1640 and 705; *E*-isomer, δ_H 7.45 (1 H, dd, *J* 1.08 and 5.12), 7.19 (1 H, *J* 3.51), 7.08–7.04 (1 H, m), 6.55 (1 H, q, *J* 1.24) and 1.27 (9 H, s); δ_F −10.7 (3 F, s). *Z*-Isomer, δ_H 7.37–7.33 (1 H, m), 7.08–7.04 (2 H, m), 6.45 (1 H, s) and 1.53 (9 H, s); δ_F −17.0 (3 F, s); *m*/*z* 278 (M^+, 3), 223 (26), 222 (56), 205 (60), 189 (19), 177 (15), 157 (19), 153 (56) and 56 (100) (Found: C, 51.4; H, 4.8. $C_{12}H_{13}F_3O_2S$ requires C, 51.79; H, 4.70).

General Procedure for the Preparation of O-*Methylated Products* **5a**, **5e** *and* **5f**.—The procedure was similar to that of method A. Before protonation, methyl iodide (5 mmol) was added to the reaction mixture which was then allowed to warm to room temperature before being stirred overnight. Evaporation of the mixture gave a residue which was separated by column chromatography on silica gel eluting with light petroleum (b.p. 60–90 °C)–ethyl acetate (4:1) to afford the products **5**. Yields were calculated on the basis of the isolated products and are reported in Table 2. Their physical and spectral data are described below.

4,4,4-*Trifluoro*-3-*methoxy*-3-*phenyl*-2-(*triphenylphosphoranylidene*)*butanenitrile* **5a**. M.p. 190–191 °C (decomp.); ν_{max}(KBr)/cm^{-1} 2140, 1435, 1200–1400 and 690; δ_H 7.55–7.31 (20 H, m) and 3.22 (3 H, s); δ_F −8.0 (3 F, s); δ_P 22.7; *m*/*z* 489 (M^+, 7), 458 (23), 420 (100) and 262 (22) (Found: C, 71.0; H, 4.8; N, 2.8. $C_{29}H_{23}F_3NOP$ requires C, 71.16; H, 4.74; N, 2.86).

Ethyl 4,4,4-*trifluoro*-3-*methoxy*-3-(2-*thienyl*)-2-(*triphenylphosphoranylidene*)*butanoate* **5e**. Obtained as a brown oil; ν_{max}(film)/cm^{-1} 3040, 1725, 1660, 1200–1140 and 690; δ_H 7.70–6.70 (18 H, m), 3.40 (2 H, q, *J* 7.3), 2.47 (3 H, s) and 0.47 (3 H, t, *J* 7.3); δ_F −7.7 (3 F, s); *m*/*z* 542 (M^+, 24), 511 (20), 497 (5), 476 (7), 474 (20), 473 (100), 369 (7), 303 (17) and 262 (65) (Found: C: 64.05; H, 4.7. $C_{29}H_{26}F_3O_3PS$ requires C, 64.20; H, 4.83).

tert-*Butyl* 4,4,4-*trifluoro*-3-*methoxy*-3-*phenyl*-2-(*triphenylphosphoranylidene*)*butanoate* **5f**. M.p. 161–162 °C; ν_{max}(KBr)/cm^{-1} 1650, 1440, 1285, 1060 and 695; δ_H 7.54–7.30 (20 H, m), 2.38 (3 H, s) and 0.73 (9 H, s); δ_F −9.8 (3 F, s); δ_P 19.5; *m*/*z* 564 (M^+, 6), 533 (2), 495 (36), 491 (6), 439 (100), 303 (61) and 262 (31) (Found: C, 70.4; H, 6.1. $C_{33}H_{32}F_3O_3P$ requires C, 70.21; H, 5.71).

Acknowledgements

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

References

1 *Biomedicinal Aspects of Fluorine Chemistry*, eds. R. Filler and

Y. Kobayashi, Elsevier, New York, 1982; J. T. Welch, *Tetrahedron*, 1987, **43**, 3123.
2 T. Kitazume, T. Kubayashi, T. Yamamoto and T. Yamazaki, *J. Org. Chem.*, 1987, **52**, 3218.
3 (*a*) D. L. Dull, I. Baxter and H. S. Mosher, *J. Org. Chem.*, 1967, **32**, 1622; (*b*) D. J. Burton and W. M. Koppes, *J. Org. Chem.*, 1975, **40**, 3026; (*c*) H. Trabelsi, B. Bertaina and A. Cambon, *Can. J. Chem.*, 1985, **63**, 426.
4 C. D. Poulter and M. D. Satterwhite, *Biochem.*, 1977, **16**, 5470.
5 Y.-C. Shen and T.-L. Wang, *Tetrahedron Lett.*, 1990, **31**, 5925.
6 Y.-C. Shen and Y.-J. Xiang, *J. Fluorine Chem.*, 1991, **52**, 221.
7 Y.-C. Shen and T.-L. Wang, *J. Chem. Soc., Perkin Trans. 1*, 1991, 487.
8 Y.-C. Shen and S. Gao, *J. Org. Chem.*, 1993, **58**, 4564.

Paper 3/07562A
Received 24*th December* 1993
Accepted 17*th February* 1994