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The stereospecific trifluoromethylation of α-iodo-α,β-unsaturated esters: a novel synthesis of (*Z*)-α-trifluoromethyl-α,β-unsaturated esters

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Abstract

This paper describes simple and successful methods for the preparation of α-iodo-α,β-unsaturated esters. The trifluoromethylation of (*Z*)-α-iodo-α,β-unsaturated esters stereo-selectively provides (*Z*)-α-trifluoromethyl-α,β-unsaturated esters. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Trifluoromethylation; α,β-Unsaturated esters

1. Introduction

It is well known that the trifluoromethyl group has a great effect on biological activity and often confers significant changes in chemical and physical properties. Therefore, methods for the synthesis of trifluoromethylated compounds have been attracting increasing attention [1,2]. We recently described a new method for the preparation of α-trifluoromethyl-α,β-unsaturated esters through the trifluoromethylation of α-bromo-α,β-unsaturated esters [3], but the double bond was isomerized under the trifluoromethylation conditions. Herein, we report the synthesis of (*Z*)-α-trifluoromethyl-α,β-unsaturated esters via the stereospecific trifluoromethylation of α-iodo-α,β-unsaturated esters.

2. Results and discussions

2.1. Preparation of α-iodo-α,β-unsaturated esters 1

α-Halo-α,β-unsaturated esters were usually prepared by the Wittig reaction of aldehydes with haloylides [4,5] and the condensation of aldehydes with halophosphonates in the presence of base [6]. However, these methods were not suitable for preparation of α-iodo-α,β-unsaturated esters, because it is difficult to obtain the iodoylide and the α-iodo-α,β-unsaturated ester was easily dehydroiodogenated under basic conditions. Recently, Kayser [7] reported a one-pot procedure preparation of a α-iodo-α,β-unsaturated ester through the reaction of carboethoxymethylenetriphenylphosphorane, potassium carbonate, *N*-iodosuccinimide and aldehyde. We were delighted to observe that compounds **1** could be obtained in high yields by a modified Chenault's procedure [6]. Treatment of (ethoxycarbonyliodomethyl)-triphenylphosphonium iodide **2** with aldehyde in the presence of 1.0 equivalent of potassium carbonate at 40°C provided the (*Z*)-α-iodo-α,β-unsaturated ester **1** as the major product (Scheme 1 and Table 1). Compound **2** was obtained from commercial (ethoxycarbonylmethyl)triphenylphosphonium bromide **3** by direct iodination in methanol in the presence of potassium carbonate (Scheme 1). The *Z*- and *E*-isomers of compounds **1c–e** can be separated by column chromatography, but other *Z*- and *E*-isomers of α-iodo-α,β-unsaturated esters could not be separated by column chromatography and the mixtures were used directly in the next trifluoromethylation reaction.

2.2. Synthesis of α-trifluoromethyl-α,β-unsaturated esters 4

The synthesis of α-trifluoromethyl-α,β-unsaturated esters **4** was based on the trifluoromethylation of α-iodo-α,β-unsaturated esters **1** (Scheme 2). Treatment of a 88:12 mixture of *Z*- and *E*-**1a** with $FSO_2CF_2CO_2Me$ and CuI in

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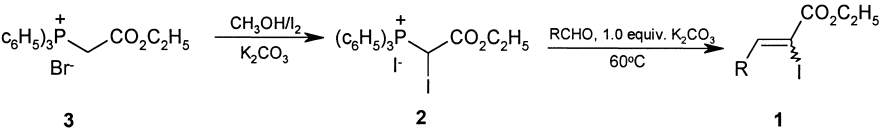
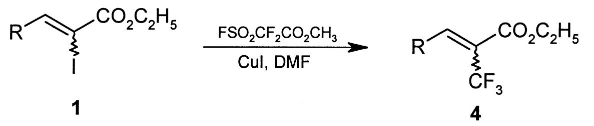


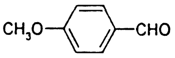
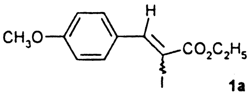
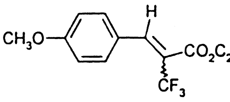
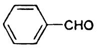
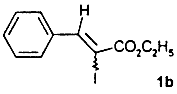
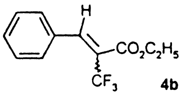
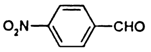
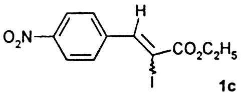
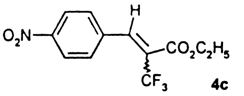
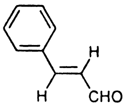
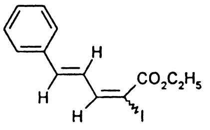
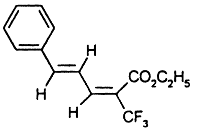
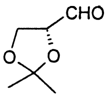
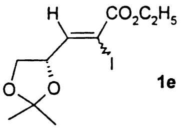
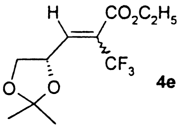
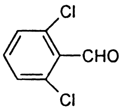
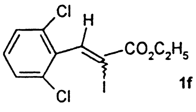
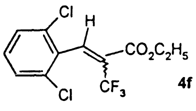
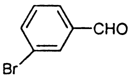
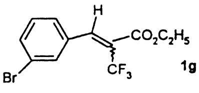
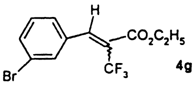
Scheme 1.



Scheme 2.

DMF/HMPA at 70°C gave a 88:12 mixture of *Z*- and *E*-**4a** in 89%. Various iodoalkenes **1** were used for the preparation of α-trifluoromethyl-α,β-unsaturated esters **4** under the same reaction conditions (Table 1). The configuration of double bond in **4** was determined by the chemical shifts of the alkenyl proton. The alkenyl proton in the *Z* isomer appeared at lower field than in the *E* isomer. The following points

Table 1
Synthesis of α-trifluoromethyl-α,β-unsaturated esters **4** via trifluoromethylation of α-iodo-α,β-unsaturated esters **1**

Entry	Aldehyde	Intermediate **1** (yield (%)[a], *Z*:*E*[b])	Product **4** (yield (%)[c], *Z*:*E*[d])
1		 **1a** 75; 88:12	 **4a** 89; 88:12
2		 **1b** 87; 81:19	 **4b** 96; 86:14
3		 **1c** 76; 84:16	 **4c** 82; 84:16
4		 **1d** 81; 90:10	 **4d**[e] 91
5		 **1e** 53; 89:11	 **4e** 81; 90:10
6		 **1f** 65; 96:4	 **4f** 92; 95:5
7		 **1g** 75; 83:17	 **4g** 92; 82:18

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[a] Yields based on aldehydes.
[b] This ratio was determined by ^1H NMR.
[c] Yields based on **1**.
[d] The ratio was determined by ^{19}F NMR.
[e] This compound was prepared from the *Z*-**1c**.

derived from the trifluoromethylation are noteworthy: (1) slow addition via syringe and an excess of $FSO_2CF_2CO_2Me$ (2.0 eq) were necessary for the total conversion of α-iodo-α,β-unsaturated esters **1**; (2) the configuration of double bonds in this reaction remained intact. Only *Z*-**4d** was formed from *Z*-**1d** (entry 4). When a mixture of *Z*- and *E*-isomers of compound **1** was used for the trifluoromethylation, the *Z*:*E* ratio of compound **4** did not change; (3) the carbon-iodide bond was more active than a carbon-bromine bond, this difference of reactivity has made the chemoselective trifluoromethylation possible with **1g** (entry 7).

3. Experimental

^{1}H NMR spectra were recorded on 300 MHz spectrometer with Me_4Si as internal standard. ^{19}F NMR spectra were obtained on a 56.4 MHz spectrometer using trifluoroacetic acid as external standard, downfield shifts being designated as negative. All chemical shifts (δ) are expressed in parts per million, coupling constants (J) are given in Hertz. Mass spectra were obtained using EI ionization at 70 eV. IR spectra were recorded on a Shimadzu IR-440 spectrometer.

3.1. General procedure for synthesis of iodo esters 1

A suspension of (ethoxycarbonyliodomethyl)triphenylphosphonium iodide (1.21 g, 2 mmol) and aldehyde (2 mmol) in 20 ml of methanol was stirred at 40°C. Potassium carbonate (138 mg, 1 mmol) was added in three portions to the suspension. The color of the mixture turned to dark brown and the suspension dissolved completely. The reaction mixture was stirred at 40°C for 8 h. After removal of methanol, the residue was purified by column chromatography on silica gel and elution with 25:1 hexane ethyl acetate to gave iodo ester **1**.

1a: Oil. IR (thin film): 2981, 1712, 1606, 1511, 1254, 1176 cm^{-1}; δ_H ($CDCl_3$, 300 MHz) 8.25 (s, 0.88H), 8.04 (d, $J = 8.1$ Hz, 0.24H), 7.88 (d, $J = 8.1$ Hz, 1.76H), 6.95 (d, $J = 8.1$ Hz, 2H), 6.94 (s, 0.12H), 4.35 (q, $J = 7.1$ Hz, 2H), 3.88 (s, 3H), 1.40 (t, $J = 7.1$ Hz, 3H); *m/z* (EI) 333 ($M^+ + 1$, 47.00), 332 (M^+, 100.00), 287 (46.44), 205 (40.78), 127 (1.79).

1b: Oil. IR (thin film): 2982, 1717, 1599, 1233, 1035 cm^{-1}; δ_H ($CDCl_3$, 300 MHz) 8.28 (s, 0.81H), 7.80 (m, 2H), 7.45 (s, 0.19H), 7.32 (m, 1H), 4.35 (q, $J = 7.1$ Hz, 1.62H), 4.20 (q, $J = 7.1$ Hz, 0.38H), 1.40 (t, $J = 7.1$ Hz, 2.43H), 1.20 (t, $J = 7.1$ Hz, 0.57H); *m/z* (EI) 303 ($M^+ + 1$, 71.31), 302 (M^+, 100.00), 257 (44.85), 175 (90.98), 127 (3.77).

1c: Solid. IR (KBr): 2987, 1716, 1610, 1520, 1347, 1251 cm^{-1}; δ_H ($CDCl_3$, 300 MHz) 8.28 (m, 2.52H), 7.85 (d, $J = 8.9$ Hz, 1.68H), 7.72 (m, 0.48H), 6.58 (d, $J = 8.9$ Hz, 0.32H), 4.38 (q, $J = 7.1$ Hz, 2H), 1.42 (t, $J = 7.1$ Hz, 3H); *m/z* (EI) 348 ($M^+ + 1$, 56.42), 347 (M^+, 63.53), 302 (20.44), 220 (70.99), 192 (100.00).

(Z)-1d: Oil. IR (thin film): 2982, 1708, 1613, 1258, 1226, 1149 cm^{-1}; δ_H ($CDCl_3$, 300 MHz) 7.80 (d, $J = 9.2$ Hz, 1H), 7.68 (m, 2H), 7.40 (m, 3H), 7.15 (d, 2H), 4.35 (q, $J = 7.1$ Hz, 2H), 1.38 (t, $J = 7.1$ Hz, 3H); *m/z* (EI) 329 ($M^+ + 1$, 13.35), 328 (M^+, 40.10), 202 (14.10), 173 (9.52), 129 (100.00), 127 (59.95).

1e: Oil. IR (thin film): 2987, 1720, 1372, 1241, 1062, 1031 cm^{-1}; δ_H ($CDCl_3$, 300 MHz) 7.38 (d, $J = 8.1$ Hz, 0.89H), 7.08 (d, $J = 8.1$ Hz, 0.11H), 4.85 (m, 1H), 4.28 (m, 3H), 3.68 (m, 1H), 1.45–1.25 (m, 9H); *m/z* (EI) 327 ($M^+ + 1$, 20.64), 311 (67.20), 269 (100.00), 127 (4.51).

1f: Oil. IR (thin film): 2984, 1722, 1429, 1305, 1189, 1035 cm^{-1}; δ_H ($CDCl_3$, 300 MHz) 7.78 (d, $J = 16.4$ Hz, 1H), 7.26 (m, 1H), 7.15 (m, 1H), 6.58 (d, $J = 16.4$ Hz, 1H), 4.32 (q, $J = 7.1$ Hz, 1.92H), 4.08 (q, $J = 7.1$ Hz, 0.08H), 1.38 (t, $J = 7.1$ Hz, 2.88H), 1.13 (t, $J = 7.1$ Hz, 0.12H); *m/z* (EI) 373 ($M^+ + 2$, 2.01), 371 (M^+, 3.13), 244 (5.54), 181 (100.00), 127 (14.36).

1g: Oil. IR (thin film): 2979, 1711, 1640, 1312, 1179, 1035 cm^{-1}; δ_H ($CDCl_3$, 300 MHz) 7.70 (s, 1H), 7.50 (m, 2H), 7.25 (m, 1H), 6.48 (d, $J = 15.7$ Hz, 1H), 4.35 (q, $J = 7.1$ Hz, 0.34H), 4.28 (q, $J = 7.1$ Hz 1.66H), 1.35 (t, $J = 7.1$ Hz, 3H); *m/z* (EI) 382/380 (M^+, 24.44), 337/335 (8.63), 211 (92.11), 209 (100.00), 127 (3.84).

3.2. General procedure for the synthesis of esters 4

A solution of $FSO_2CF_2CO_2CH_3$ (0.5 ml, 4 mmol) in DMF (10 ml) was added dropwise over a period of 3 h to a mixture of ester 1(2 mmol), CuI(96 mg, 0.5 mmol) and HMPA(1 ml) in DMF(15 ml) at 65°C. The reaction was stirred at 65°C for 10 h before being cooled to room temperature. Saturated aqueous NH_4Cl (30 ml) was added and the mixture was extracted with ether. The extracts were washed with brine and dried over Na_2SO_4. The solvent was removed in vacuo. Purification of the residue by column chromatography on silica gel and elution with 25:1 hexane ethyl acetate gave compounds **4**.

4a: Oil. IR (thin film): 2982, 1726, 1606, 1514, 1265, 1178 cm^{-1}; δ_H ($CDCl_3$, 300 MHz) 7.99 (s, 0.88H), 7.41 (d, $J = 9.5$ Hz, 2H), 7.25 (s, 0.12H), 6.91 (m, 2H), 4.34 (m, 2H), 3.83 (s, 3H), 1.37 (t, $J = 7.1$ Hz, 3H); δ_F ($CDCl_3$, 56.4 MHz) −20.6 (s, 2.64F), −15.2 (s, 0.36F); *m/z* (EI) 275 ($M^+ + 1$, 18.44), 274 (M^+, 100.00), 205 (8.41), 69 (12.45); Anal. Calc. for $C_{13}H_{13}F_3O_3$: C, 56.94; H, 4.78. Found: C, 56.88; H, 4.74%.

4b: Oil. IR (thin film): 2988, 1733, 1641, 1400, 1279 cm^{-1}; δ_H ($CDCl_3$, 300 MHz) 8.05 (s, 0.88H), 7.36 (s, 0.14H), 7.35 (s, 5H), 4.26 (q, $J = 7.1$ Hz, 2H), 1.30 (t, $J = 7.1$ Hz, 3H); δ_F ($CDCl_3$, 56.4 MHz) −19.7 (s, 2.58F), −13.7 (s, 0.42F); *m/z* (EI) 245 ($M^+ + 1$, 11.91), 244 (M^+, 65.47), 199 (100.00), 175 (3.25), 69 (4.95).

4c: Solid. IR (KBr): 2992, 1722, 1639, 1521, 1349, 1282 cm^{-1}; δ_H ($CDCl_3$, 300 MHz) 8.27 (d, $J = 9.0$ Hz, 2H), 8.10 (s, 0.84H), 7.54 (d, $J = 9.0$ Hz, 2H), 7.53 (s, 0.16H), 4.25 (q, $J = 7.0$ Hz, 2H), 1.38 (t, $J = 7.0$ Hz, 3H); δ_F (CDCl$_3$, 56.4 MHz) −19.0 (s, 2.52F), −12.6 (s, 0.48F); *m/z* (EI) 290 ($M^+ + 1$, 11.58), 289 (M^+, 25.70), 244 (100.00), 69 (9.49); Anal. Calc. for $C_{12}H_{10}F_3NO_4$: C, 49.83; H, 3.49; N, 4.84. Found: C, 49.80; H, 3.59; N, 4.84%.

(**Z**)-**4d**: Oil. IR (thin film): 2987, 1724, 1623, 1290, 1257, 1140 cm^{-1}; δ_H (CDCl$_3$, 300 MHz) 7.72 (d, $J = 11.9$ Hz, 1H), 7.53 (m, 2H), 7.41 (m, 4H), 7.11 (d, $J = 15.2$ Hz, 1H), 4.33 (q, $J = 7.1$ Hz, 2H), 1.35 (t, $J = 7.1$ Hz, 3H); δ_F (CDCl$_3$, 56.4 MHz) −20.7 (s, 3F); *m/z* (EI) 271 ($M^+ + 1$, 49.49), 270 (M^+, 100.00), 225 (26.47), 69 (12.31).

4e: Oil. IR (thin film): 2991, 1737, 1375, 1264, 1149 cm^{-1}; δ_H (CDCl$_3$, 300 MHz) 7.30 (d, $J = 7.0$ Hz, 1H), 5.10 (m, 1H), 4.27 (m, 3H), 3.72 (m, 1H), 1.48–1.26 (m, 9H); δ_F (CDCl$_3$, 56.4 MHz) −11.9 (s, 2.70F), −17.6 (s, 0.30F); *m/z* (EI) 269 ($M^+ + 1$, 9.58), 253 (58.69), 69 (4.09), 42 (100.00); Anal. Calc. for $C_{11}H_{15}F_3O_4$: C, 49.25; H, 5.60. Found: C, 49.22; H, 5.79%.

4f: Oil. IR (thin film): 2984, 1719, 1645, 1430, 1308, 1189 cm^{-1}; δ_H (CDCl$_3$, 300 MHz) 7.72 (d, $J = 16.4$ Hz, 1H), 7.26 (m, 1H), 7.10 (m, 1H), 6.55 (d, $J = 16.4$ Hz, 1H), 4.25 (q, $J = 7.1$ Hz, 2H), 1.25 (t, $J = 7.1$ Hz, 3H); δ_F (CDCl$_3$, 56.4 MHz) −19.6 (s, 2.85F), −14.8 (s, 0.15F); *m/z* (EI) 315 ($M^+ + 2$, 1.57), 313 (M^+, 1.81), 245 (36.54), 209 (100.00), 69 (3.08).

4g: Oil. IR (thin film): 2986, 1733, 1642, 1288, 1267, 1141 cm^{-1}; δ_H (CDCl$_3$, 300 MHz) 8.15 (s, 1H); 7.58 (m, 2H); 7.30 (m, 1H), 6.48 (d, $J = 15.8$ Hz, 1H), 4.32 (q, $J = 7.1$ Hz, 2H), 1.42 (t, $J = 7.1$ Hz, 3H); δ_F (CDCl$_3$, 56.4 MHz) −19.7 (s, 2.46F), −13.0 (s, 0.54F); *m/z* (EI) 325/323 ($M^+ + 1$, 0.97), 324/322 (M^+, 0.78), 279/277 (11.86), 195 (100.00), 69 (2.31).

Acknowledgements

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