A convenient palladium-catalyzed synthesis of α-fluoro-α,β-unsaturated esters

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Abstract

During the treatment of ethyl α-fluoro-α-iodoacetate with aldehydes in the presence of tri-n-butylarsine and a catalytic amount (10 mol%) of $Pd(PPh_3)_4$, the aldehydes were eventually completely consumed and α-fluoro-α,β-unsaturated esters were obtained in 52–90% yield.

Introduction

α-Fluoro-α,β-unsaturated esters have attracted much interest since they can serve as useful intermediates in organic synthesis, particularly for biologically active compounds. Substitution of a fluorine atom adjacent to the ester functionality usually increases the biological activity of these compounds significantly, as exemplified in vitamin A and pheromone chemistry [1]. They have been used successfully as intermediates in the synthesis of monofluorinated retinoids, insect sex pheromones and pyrethroids [2]. The reaction of carbonyl compounds with fluoroacetate or fluorooxaloacetate gave a mixture of products in low yield [3]. Thenappan and Burton reported a reduction–olefination sequence which converted esters to α-fluoro-α,β-unsaturated esters in 44–76% yields [2]. However, effective methods available for their preparation are relatively few [4].

Results and discussion

Recently, we reported a palladium-catalyzed reaction of bromoacetic ester with aldehydes in the presence of tri-n-butylphosphine leading to the conversion of aldehydes to α,β-unsaturated esters with high stereoselectivity in 52–85% yield [5]. As an extension of this study, this methodology is applicable to the synthesis of the fluorinated analogs, α-fluoro-α,β-unsaturated esters, in good yield. The reaction may be expressed as follows:

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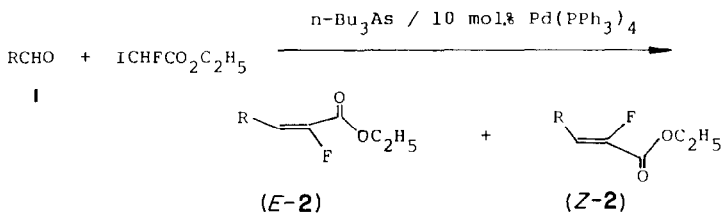
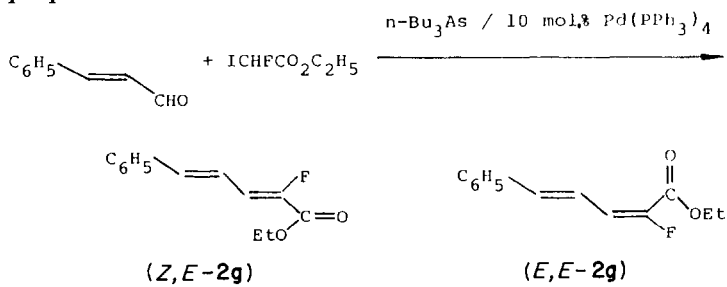


(*E*-**2**) (*Z*-**2**)

On treatment of ethyl α-fluoro-α-iodoacetate with aldehydes in the presence of tri-n-butylarsine and a catalytic amount (10 mol%) of $Pd(PPh_3)_4$, the aldehydes were eventually completely consumed and the α-fluoro-α,β-unsaturated esters were obtained in 52–90% yield. The results are listed in Table 1. On the basis of data reported in the literature [6], the chemical shift of the fluorine of the *Z* isomer is upfield and that of the *E* isomer is downfield.

The reaction is of wide scope (Table 1). The aldehydes may be aromatic, aliphatic or heterocyclic and may contain a double bond. Double bonds conjugated with the carbonyl group do not interfere, the attack being at the carbonyl carbon and giving the α-fluoro-2,4-dienyl carboxylate which is also a very useful intermediate in organic synthesis and is not otherwise easy to prepare.



(*Z,E*-**2g**) (*E,E*-**2g**)

TABLE 1

Palladium-catalyzed synthesis of ethyl α-fluoro-α,β-unsaturated esters

Compound	R	Temp. (°C)	Time (h)	Yield[a] (%)	*Z*/*E*[b]
2a	C_6H_5	110	24	85	57:43
2b	4-$NO_2C_6H_4$	100	16	90	55:45
2c	4-ClC_6H_4	100	24	82	57:43
2d	4-FC_6H_4	110	24	83	60:40
2e	4-$CH_3C_6H_4$	100	24	68	57:43
2f	4-$CH_3OC_6H_4$	110	24	63	60:40
2g	(*E*)-$C_6H_5CH{=}CH$	100	24	62	67:33[c]
2h	2-furyl	100	24	52	54:46[c]
2i	n-C_5H_{11}	110	24	56	65:35

[a]Isolated yields. All products were characterized spectroscopically.

[b]The ratios of *E* to *Z* isomers were estimated on the basis of ^{19}F NMR spectra in comparison to reported data [6].

[c]The mixture of *E* and *Z* isomer could be separated by chromatography on silica gel with petroleum ether as the eluent (b.p., 60–90 °C).

Relative to other methods reported in the literature [2], this one-pot reaction provides a new method for the convenient synthesis of the title compounds which should be useful for further elaboration in the synthesis of biologically active compounds.

Experimental

Infrared spectra were recorded on a Shimadzu IR-440 spectrometer. ^{1}H NMR spectra were determined at 200 MHz using a XL-200 spectrometer (chemical shifts are reported in ppm downfield from internal TMS); ^{19}F NMR spectra were recorded at either 90 MHz using an FX-90 spectrometer or at 60 MHz using a Varian EM-360A spectrometer (chemical shifts are reported in ppm upfield from external CF_3COOH). Ethyl chlorofluoroacetate was prepared by a literature method [7], and ethyl iodofluoroacetate was prepared by a simple Finkelstein reaction of ethyl chlorofluoroacetate [4]. $Pd(PPh_3)_4$ was prepared by a literature method [8] as was tri-n-butylarsine [9]. The aldehydes were commercially available research grade chemicals, and were redistilled or recrystallized prior to use.

General procedure for the preparation of (E)- and (Z)-α-fluoro-α,β-alkenoate esters

An oven-dried two-necked round-bottom flask was equipped with a nitrogen inlet and a magnetic stirrer, and flushed with nitrogen. Tri-n-butylarsine (2.0 mmol) was injected into a mixture consisting of aldehydes **1** (1.0 mmol), ethyl iodofluoroacetate (2.0 mmol) and $Pd(PPh_3)_4$ (0.1 mmol) under nitrogen. The mixture was stirred and heated to 110 °C (or 100 °C) for several hours (see Table 1). After reaction, chromatography on silica gel eluting with petroleum ether (b.p., 60–90 °C)/ethyl acetate (9:1) gave the pure products **2**.

Ethyl-2-fluoro-3-phenylpropenoate (**2a**) [6] was obtained in 85% yield; *Z*/*E* = 57:43. ^{19}F NMR (CCl_4) δ: 38.3 (d, *J* = 22 Hz, *E*); 47.2 (d, *J* = 35 Hz, *Z*) ppm. ^{1}H NMR ($CDCl_3$) δ: 1.23 (*E*) + 1.38 (*Z*) (t, 3H, *J* = 7.1 Hz); 4.24 (*E*) + 4.35 (*Z*) (q, 2H, *J* = 7.1 Hz); 6.90 (*E*) + 6.92 (*Z*) [d, 1H, *J* = 22 Hz (*E*), 35 Hz (*Z*)]; 7.40 (m, 5H) ppm. IR (neat) (cm^{-1}): 1735 (s, C=O); 1670 (m, C=C).

Ethyl 2-fluoro-3-(4-nitrophenyl)propenoate (**2b**) [10] was obtained in 90% yield; *Z*/*E* = 55:45. ^{19}F NMR (CCl_4) δ: 35.3 (d, *J* = 21 Hz, *E*); 42.6 (d, *J* = 34 Hz, *Z*) ppm. ^{1}H NMR ($CDCl_3$) δ: 1.26 (*E*) + 1.40 (*Z*) (t, 3H, *J* = 7.1 Hz); 4.26 (*E*) + 4.39 (*Z*) (q, 2H, *J* = 7.1 Hz); 6.92 (*E*) + 6.98 (*Z*) [d, 1H, *J* = 21 Hz (*E*), 34 Hz (*Z*)]; 7.60 (*E*) + 7.79 (*Z*) (d, 2H, *J* = 9 Hz); 8.21 (*E*) + 8.26 (*Z*) (d, 2H, *J* = 9 Hz) ppm. IR (KBr) (cm^{-1}): 1730 (s, C=O); 1670 (m, C=C).

Ethyl 2-fluoro-3-(4-chlorophenyl)propenoate (**2c**) [11] was obtained in 82% yield; *Z*/*E* = 57:43. ^{19}F NMR (CCl_4) δ: 37.2 (d, *J* = 22 Hz, *E*); 46.3 (d, *J* = 35 Hz, *Z*) ppm. ^{1}H NMR ($CDCl_3$) δ: 1.26 (*E*) + 1.38 (*Z*) (t, 3H, *J* = 7.1

Hz); 4.25 (*E*)+4.35 (*Z*) (q, 2H, J=7.1 Hz); 6.83 (*E*)+6.86 (*Z*) [d, 1H, J=22 Hz (*E*), 35 Hz (*Z*)]; 7.40 (m, 4H) ppm. IR (neat) (cm^{-1}): 1735 (s, C=O); 1660 (m, C=C).

Ethyl 2-fluoro-3-(4-fluorophenyl)propenoate (**2d**) [10] was obtained in 83% yield: *Z*/*E*=60:40. ^{19}F NMR ($CDCl_3$) δ: 34.8 (s, *E*); 39.5 (d, J=22 Hz, *E*); 32.5 (s, *Z*); 49.0 (d, J=35 Hz, *Z*) ppm. ^1H NMR ($CDCl_3$) δ: 1.26 (*E*)+1.37 (*Z*) (t, 3H, J=7.2 Hz); 4.25 (*E*)+4.34 (*Z*) (q, 2H, J=7.2 Hz); 6.86 (*E*)+6.88 (*Z*) [d, 1H, J=22 Hz (*E*), 35 Hz (*Z*)]; 7.05 (*E*)+7.10 (*Z*) (d, 2H, J=9 Hz); 7.61 (*E*)+7.64 (*Z*) (d, 2H, J=9 Hz) ppm. IR (neat) (cm^{-1}): 1740 (s, C=O); 1670 (m, C=C).

Ethyl 2-fluoro-3-(4-methylphenyl)propenoate (**2e**) [11] was obtained in 68% yield; *Z*/*E*=57:43. ^{19}F NMR (CCl_4) δ: 39.4 (d, J=22 Hz, *E*); 48.4 (d, J=34 Hz, *Z*) ppm. ^1H NMR ($CDCl_3$) δ: 1.20 (*E*)+1.30 (*Z*) (t, 3H, J=7 Hz); 2.27 (*E*)+2.28 (*Z*) (s, 3H); 4.18 (*E*)+4.26 (*Z*) (q, 2H, J=7 Hz); 6.79 (*E*)+6.82 (*Z*) [d, 1H, J=22 Hz (*E*), 34 Hz (*Z*)]; 7.08 (*E*)+7.12 (*Z*) (d, 2H, J=9 Hz); 7.30 (*E*)+7.46 (*Z*) (d, 2H, J=9 Hz) ppm. IR (neat) (cm^{-1}): 1725 (s, C=O); 1665 (m, C=C).

Ethyl 2-fluoro-3-(4-methoxyphenyl)propenoate (**2f**) [11] was obtained in 63% yield; *Z*/*E*=60:40. ^{19}F NMR (CCl_4) δ: 41.0 (d, J=22 Hz, *E*); 51.0 (d, J=35 Hz, *Z*) ppm. ^1H NMR ($CDCl_3$) δ: 1.29 (*E*)+1.37 (*Z*) (t, 3H, J=7.1 Hz); 3.81 (*E*)+3.83 (*Z*) (s, 3H); 4.28 (*E*)+4.33 (*Z*) (q, 2H, J=7.1 Hz); 6.83 (*E*)+6.87 (*Z*) [d, 1H, J=22 *Hz* (*E*), 35 Hz (*Z*)]; 6.87 (*E*)+6.91 (*Z*) (d, 2H, J=9 Hz); 7.51 (*E*)+7.59 (*Z*) (d, 2H, J=9Hz) ppm. IR (neat) (cm^{-1}): 1730 (s, C=O); 1665 (m, C=C).

Ethyl 2-fluoro-5-phenyl-(2,4)-pentadienoate (**2g**) [12] was obtained in 62% yield; (*Z*,*E*)/(*E*,*E*)=67:33. (*E*,*E*)-**2g**: ^{19}F NMR (CCl_4) δ: 45.5 (d, 1F, J=19 Hz) ppm. ^1H NMR (C_6D_6) δ: 0.96 (t, 3H, J=7.0 Hz); 3.99 (q, 2H, J=7.0 Hz); 6.34 (dd, 1H, $J_{H,F}$=19 Hz, $J_{3,4}$=11.5 Hz, H^3); 6.37 (d, 1H, $J_{5,4}$=16.0 Hz, H^5); 7.03–7.11 (m, 3H); 7.30–7.34 (m, 2H); 8.05 (dd, 1H, $J_{4,3}$=11.5 Hz, $J_{4,5}$=16.0 Hz, H^4) ppm. (*Z*,*E*)-**2g**: ^{19}F NMR (CCl_4) δ: 51.2 (d, 1F, J=31 Hz) ppm. ^1H NMR (C_6D_6) δ: 0.99 (t, 3H, J=7.1 Hz); 4.03 (q, 2H, J=7.1 Hz); 6.36 (d, 1H, J=15.3 Hz, H^5); 6.78 (dd, 1H, $J_{H,F}$=30.8 Hz, $J_{3,4}$=11.4 Hz, H^3); 6.99–7.19 (m, 6H, Ar-H, H^4) ppm. IR (neat) (cm^{-1}): 1730 (s, C=O); 1650 (m, C=C).

Ethyl 2-fluoro-3-(2-furyl)propenoate (**2h**) was obtained in 52% yield; *Z*/*E*=54:46. (*E*)-**2h**: ^{19}F NMR ($CDCl_3$) δ: 43.86 (d, 1F, J=22 Hz) ppm. ^1H NMR ($CDCl_3$) δ: 1.40 (t, 3H, J=22 Hz); 4.38 (q, 2H, J=7.2 Hz); 6.54 (m, 1H); 6.84 (d, 1H, J=22 Hz); 7.50 (m, 2H) ppm. (*Z*)-**2h**: ^{19}F NMR ($CDCl_3$) δ: 44.67 (d, 1F, J=33 Hz) ppm. ^1H NMR ($CDCl_3$) δ: 1.36 (t, 3H, J=7.2 Hz); 4.34 (q, 2H, J=7.2 Hz); 6.54 (m, 1H); 6.86 (m, 1H); 6.94 (d, 1H, J=33 Hz); 7.52 (m, 1H) ppm. IR (neat) (cm^{-1}): 1730 (s, C=O); 1670 (s, C=C). MS *m*/*e*: 184 (M^+, 100.0); 185 (13.4); 156 (71.4); 139 (34.7); 112 (17.3); 80 (8.7). Analysis: Calcd. for $C_9H_9FO_3$: C, 58.696; H, 4.891%. Found: C, 58.39; H, 5.19%.

Ethyl 2-fluoro-2-octenoate (**2i**) [2] was obtained in 56% yield; *Z*/*E*=57:43. ^{19}F NMR ($CDCl_3$) δ: 44.3 (d, J=22 Hz, *E*); 52.6 (d, J=32 Hz, *Z*) ppm. ^1H

NMR ($CDCl_3$) δ: 0.92 (t, 3H, $J=6$ Hz); 1.32 (m, 9H); 2.2 (m, 2H, $J=8$ Hz); 4.28 (q, 2H, $J=7$ Hz); 6.08 (*E*)+6.12 (*Z*) [dt, 1H, $J_{H,F}=22$ Hz (*E*), 32 Hz (*Z*)] ppm. IR (neat) (cm^{-1}): 1740 (s, C=O); 1680 (m, C=C).

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