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Stereoselective synthesis of (*Z*)-β-fluoro-α,β-unsaturated esters from (*Z*)-2-fluoro-1-alkenyliodonium salts

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Abstract

(*Z*)-β-Fluoro-α,β-unsaturated esters were stereoselectively synthesized from (*Z*)-2-fluoro-1-alkenyliodonium salts by the Pd-catalyzed methoxycarbonylation reaction. The reaction proceeded at room temperature and various functional groups on the substrate can tolerate the reaction conditions.

Keywords: (Z)-2-fluoro-1-alkenyliodonium salts, (Z)-β-fluoro-α,β-unsaturated esters, Methoxycarbonylation reaction, Pd catalyst

1. Introduction

α-Fluoro-α,β-unsaturated esters have been used as building blocks or key intermediates for the synthesis of the fluorinated analogs of natural compounds having a fluorine atom on their double bonds because they can be stereoselectively prepared by the Horner-Wadsworth-Emmons reaction using ethyl 2-fluorodiethylphosphonoacetate [1-8]. On the other hand, only few methods had been reported for the stereoselective synthesis of β-fluoro-α,β-unsaturated esters [9]. Recently, we reported the stereoselective synthesis of (*E*)-isomer of β-fluoro-α,β-unsaturated esters by methoxycarbonylation of (*E*)-2-fluoro-1-alkenyliodonium salts obtained from 1-alkynes and iodotoluene difluoride [10,11].[3] However, the stereoselective synthesis of the (*Z*)-isomer of β-fluoro-α,β-unsaturated esters still remained undeveloped. Quite recently, we found that (*Z*)-2-fluoro-1-alkenyliodonium salts (**1**) can be stereoselectively prepared from 1-alkynyl(phenyl)iodonium salts [12]. We now report here the stereoselective synthesis of the (*Z*)-isomer of β-fluoro-α,β-unsaturated esters (**2**) from

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the (*Z*)-2-fluoro-1-alkenyliodonium salts (**1**) (Eq. (1)).

(eq 1)

2. Results and discussion

The methoxycarbonylation reaction of (*Z*)-2-fluoro-1-dodecenyl(phenyl)iodonium tetrafluoroborate (**1a**) was carried out using $PdCl_2$ as a catalyst and Et_3N as base which were used in the reaction of (*E*)-isomers [11]. The reaction was completed in 2 h at room temperature and the desired methyl (*Z*)-2-fluoro-2-tridecenoate (**2a**) could be obtained in 70% yield based on **1a** with high stereoselectivity (Z>98%). The yield of **2a** could be slightly improved (73%) by the use of $NaHCO_3$ instead of Et_3N, but application of other Pd catalyst could not improve the results. The stereochemistry of the double bond in **2a** was determined from NMR. A coupling constant value between F and H at C 2 is 31.1 Hz in **2a** which is larger than that of (*E*)-isomer (J = 19.1 Hz) [9] and support that F and H are in *trans*-relationship on double bond [9]. Under the reaction conditions, functional groups such as an ester, ketone, chloride remained unchanged and various (*Z*)-β-fluoro-α,β-unsaturated esters could be synthesized in good yields as shown in Table 1.

(Table 1)

3. Conclusion

We succeeded to synthesize (*Z*)-β-fluoro-α,β-unsaturated esters (**2**) stereoselectively by the Pd catalyzed methoxycarbonylation reaction of the (*Z*)-2-fluoro-1-alkenyliodonium salts (**1**). As we previously succeeded in the stereoselective synthesis of (*E*)-β-fluoro-α,β-unsaturated esters, now both (*E*)- and (*Z*)-isomers of β-fluoro-α,β-unsaturated esters can be stereoselectively prepared.

4. Experimental

4.1. General methods

The IR spectra were recorded using a JASCO FT/IR-410. The ^{1}H-NMR (400 MHz), ^{19}F-NMR (376 MHz) and ^{13}C-NMR (100 MHz) spectra were recorded in $CDCl_3$ on a JEOL JNM-A400II FT NMR and the chemical shifts, δ, are referred to TMS (^{1}H, ^{13}C) and $CFCl_3$ (^{19}F). The EI or FAB low- and high-resolution mass spectra was measured on a JEOL JMS-700TZ, JMS-FAB mate or JMS-HX110. The elemental microanalysis was done using a Yanagimoto CHN Corder MT-5. Hydrofluoric acid of 46% in water was purchased from Wako Chemical Co., Inc., and diluted to 20% with distilled water. The 1-alkynyl(phenyl)iodonium tetrafluoroborates **1** were prepared from the corresponding alkynes [13].

*4.2. Preparation of (Z)-2-fluoro-1-dodecenyl(phenyl)iodonium tetrafluoroborate (**1a**).*

In a Teflon^{TM} PFA vessel were placed 1-dodecynyl(phenyl)iodonium tetrafluoroborate (228 mg, 0.5 mmol) [13], a 20% hydrofluoric acid (500 mg, 5 mmol), and $CHCl_3$ (2 ml) and the mixture was vigorously stirred for 6 h at 60 ºC. The reaction mixture was poured into a 5% aqueous solution of $NaBF_4$ (20 ml) and extracted with CH_2Cl_2 (10 ml) four times. The combined organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by recrystallization from CH_2Cl_2-hexane and dried in vacuo to give **1a** in 84% yield (200 mg, 0.42 mmol): mp 27-28 °C. IR (KBr): ν 3061, 3048, 2956 cm^{-1}. ^{1}H NMR δ 0.88 (t, 3H, J=7.3 Hz), 1.19-1.31 (m, 14H), 1.52-1.60 (m, 2H), 2.57 (dt, 2H, $^3J_{H\text{-}F}$=17.3, J=7.6 Hz), 6.52 (d, 1H, $^3J_{H\text{-}F(olefin)}$=33.2 Hz), 7.45-8.02 (m, 5H). ^{19}F NMR δ -63.90 (d, $^3J_{H\text{-}F(olefin)}$=33.2 Hz). ^{13}C NMR δ 14.11, 22.67, 25.48, 28.69, 29.03, 29.26, 29.35, 29.47, 31.86, 32.26 (d, $^2J_{C\text{-}F}$=23.2 Hz), 74.20 (d, $^2J_{C\text{-}F}$=21.5 Hz), 111.40, 132.28 (2C), 132.64, 135.27 (2C), 174.19 (d, $^1J_{C\text{-}F}$=280.0 Hz). Anal. calcd. for $C_{18}H_{27}BF_5I$; C, 45.41; H, 5.72. Found: C, 45.48; H, 5.85.

*4.3.1. Synthesis of methyl (Z)-3-fluoro-2-tridecenoate (**2a**).*

In a flask fitted with a balloon (3 L) were placed $PdCl_2$ (1.8 mg, 0.01 mmol), $NaHCO_3$ (42 mg, 0.5 mmol) and MeOH (4 ml). After the complete replacement of the atmosphere in the flask with CO, the balloon was filled with CO. Then a solution of **1a** (238 mg, 0.5 mmol) in MeOH (1 ml) was added. After stirring for 2 h at room temperature, the reaction mixture was poured into 15% aq. NH_4Cl (15 ml), and extracted with diethyl ether (10 ml) three times. The combined organic phase was dried over $MgSO_4$, and concentrated under reduced pressure. Purification by column chromatography (silica gel/hexane-diethyl ether) gave **2a** in 73% yield (89 mg, *Z* / *E* > 98 / 2). IR: (neat) ν 2926, 1735, 1685, 1217 cm^{-1}. ^{1}H NMR δ 0.88 (t, 3H, J = 7.1 Hz), 1.21-1.37 (m, 14H), 1.52-1.59 (m, 2H), 2.26 (dt, 2H, $^{3}J_{H\text{-}F}$ = 17.3, J = 7.6 Hz), 3.72 (s, 3H), 5.18 (d, 1H, $^{3}J_{H\text{-}F(olefin)}$ = 33.1 Hz); ^{19}F NMR δ -79.53 (dt, 1F, $^{3}J_{H\text{-}F}$ = 17.3, $^{3}J_{H\text{-}F(olefin)}$ = 33.1 Hz). ^{13}C NMR δ 14.11, 22.68, 25.54, 28.80, 29.21, 29.29, 29.42, 29.53, 31.88, 32.98 (d, $^{2}J_{C\text{-}F}$ = 24.1 Hz), 51.33, 98.38 (d, $^{2}J_{C\text{-}F}$ = 6.0 Hz), 164.30, 172.40 (d, $^{1}J_{C\text{-}F}$ = 281.1 Hz). HRMS (EI) calc. for $C_{13}H_{22}FO$ (M^{+}-OMe): 213.1655. found: 213.1648.

4.3.2. Methyl (Z)-4-cyclohexyl-3-fluoro-2-propenoate (**2b**).

Yield 64% (*Z* / *E* > 98 / 2). IR: (neat) ν 1726, 1662, 1166 cm^{-1}. ^{1}H NMR δ 3.80 (s, 3H), 5.92 (d, 1H, $^{3}J_{H\text{-}F(olefin)}$ = 33.4 Hz), 7.42-7.68 (m, 5H). ^{19}F NMR δ -96.25 (d, $^{3}J_{H\text{-}F(olefin)}$ = 33.4 Hz). ^{13}C NMR δ 51.59, 96.75 (d, $^{2}J_{C\text{-}F}$ = 7.4 Hz), 125.61 (d, 2C, $^{3}J_{C\text{-}F}$ = 8.2 Hz), 128.86 (2C), 130.51 (d, $^{2}J_{C\text{-}F}$ = 25.6 Hz), 131.55, 164.48, 166.41 (d, $^{1}J_{C\text{-}F}$ = 277.6 Hz). HRMS (EI): calc. for $C_{10}H_9FO_2$: 180.0586 found: 180.0586.

*4.3.3. Methyl (Z)-3-fluoro-3-phenylpropenoate (**2c**).*

Yield 70% (*Z* / *E* > 98 / 2). IR: (neat) ν 2926, 1732, 1683, 1218 cm^{-1}. ^{1}H NMR δ 0.91-1.00 (m, 2H), 1.09-1.31 (m, 3H), 1.59-1.77 (m, 6H), 2.14 (dd, 2H, $^{3}J_{H\text{-}F}$ = 20.9, J = 7.1 Hz), 3.72 (s, 3H), 5.16 (d, 1H, $^{3}J_{H\text{-}F(olefin)}$ = 32.9 Hz). ^{19}F NMR δ -78.63 (dt, $^{3}J_{H\text{-}F}$ = 20.9, $^{3}J_{H\text{-}F(olefin)}$ = 32.9 Hz). ^{13}C NMR δ 25.93 (2C), 26.09, 32.82 (2C), 34.87, 40.85 (d, $^{2}J_{C\text{-}F}$ = 23.1 Hz), 51.27, 99.45 (d, $^{2}J_{C\text{-}F}$ = 5.7 Hz), 164.18, 171.26 (d, $^{1}J_{C\text{-}F}$ = 286.6 Hz). HRMS (EI): calc. for $C_{11}H_{17}FO_2$: 200.1213 found: 200.1214.

*4.3.4. Methyl (Z)-12-chloro-3-fluoro-2-dodecenoate (**2d**).*

Yield 67% (*Z* / *E* > 98 / 2). IR: (neat) ν 2931, 1732, 1685, 1218 cm^{-1}. ^{1}H NMR δ 1.30-1.44 (m, 10H), 1.52-1.60 (m, 2H), 1.73-1.80 (m, 2H), 2.27 (dt, 2H, $^{3}J_{H\text{-}F}$ = 17.3, J = 7.6 Hz), 3.53 (t, 2H, J = 6.8 Hz), 3.72 (s, 3H), 5.18 (d, 1H, $^{3}J_{H\text{-}F(olefin)}$ = 33.1 Hz). ^{19}F NMR δ -79.61 (dt, $^{3}J_{H\text{-}F}$ = 17.3, $^{3}J_{H\text{-}F(olefin)}$ = 33.1 Hz). ^{13}C NMR δ 25.50, 26.79, 28.70, 28.76, 29.05, 29.19, 32.57, 32.93 (d, $^{2}J_{C\text{-}F}$ = 23.1 Hz), 45.10, 51.30, 98.42 (d, $^{2}J_{C\text{-}F}$ = 4.9

Hz), 164.24, 172.29 (d, $^{1}J_{C\text{-}F}$ = 285.8 Hz). HRMS (FAB) calc. for $C_{13}H_{23}ClFO_2$ ($M^{+}+H$): 265.1371 found: 265.1390.

*4.3.5. Methyl (Z)-3-fluoro-11-(2-propoxycarbonyl)-2-undecenoate (**2e**).*

Yield 66% (*Z* / *E* > 98 / 2). IR: (neat) ν 2933, 1731, 1684, 1218 cm^{-1}. ^{1}H NMR δ 1.19-1.27 (m, 14H), 1.49-1.59 (m, 4H), 2.19-2.27 (m, 4H), 3.69 (s, 3H), 4.92-5.02 (m, 1H), 5.15 (d, 1H, $^{3}J_{H\text{-}F(olefin)}$ = 33.2 Hz). ^{19}F NMR δ -79.60 (dt, $^{3}J_{H\text{-}F}$ = 17.7, $^{3}J_{H\text{-}F(olefin)}$ = 33.2 Hz). ^{13}C NMR δ 21.82 (2C), 24.92, 25.49, 28.68, 28.97 (2C), 29.00, 32.92 (d, $^{2}J_{C\text{-}F}$ = 23.9 Hz), 34.63, 51.28, 67.32, 98.39 (d, $^{2}J_{C\text{-}F}$ = 5.7 Hz), 164.24, 172.28 (d, $^{1}J_{C\text{-}F}$ = 286.6 Hz), 173.32. HRMS (EI): calc. for $C_{16}H_{27}FO_4$: 302.1893 found: 302.1878.

*4.3.6. Methyl (Z)-3-fluoro-13,13-dimethyl-12-oxo-2-tetradecenoate (**2f**).*

Yield 68% (*Z* / *E* > 98 / 2). IR: (neat) ν 2932, 1734, 1704, 1685, 1219 cm^{-1}. ^{1}H NMR δ 1.10 (s, 9H), 1.20-1.32 (m, 8H), 1.47-1.56 (m, 4H), 2.23 (dt, 2H $^{3}J_{H\text{-}F}$ = 17.3, *J* = 7.8 Hz), 2.43 (t, 2H, *J* = 7.3 Hz), 3.69 (s, 3H), 5.15 (d, 1H, $^{3}J_{H\text{-}F(olefin)}$ = 33.4 Hz). ^{19}F NMR δ -79.59 (dt, $^{3}J_{H\text{-}F}$ = 17.3, $^{3}J_{H\text{-}F(olefin)}$ = 33.4 Hz). ^{13}C NMR δ 23.82, 25.50, 26.38 (3C), 28.70, 29.02, 29.18, 29.26, 32.92 (d, $^{2}J_{C\text{-}F}$ = 23.9 Hz), 36.34, 44.06, 51.28, 98.39 (d, $^{2}J_{C\text{-}F}$ = 4.9 Hz), 164.24, 172.33 (d, $^{1}J_{C\text{-}F}$ = 283.3 Hz), 216.04. HRMS (EI): calc. for $C_{17}H_{29}FO_3$: 300.2101 found: 300.2109.

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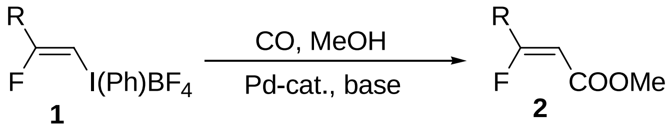
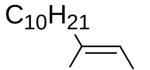
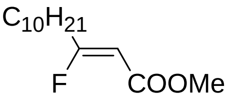
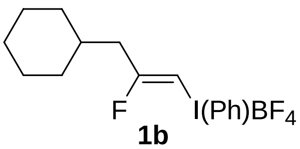
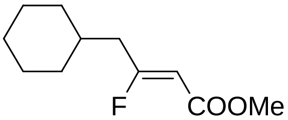
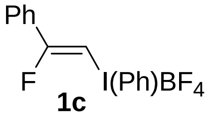
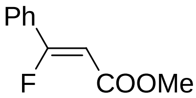
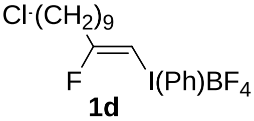
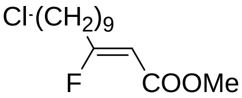
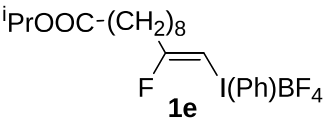
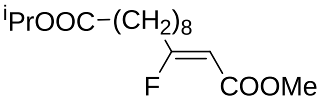
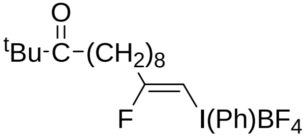
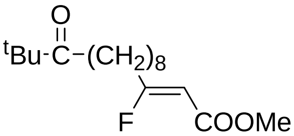


(1)

Table 1 Stereoselective synthesis of (*Z*)-β-fluoro-α,β-unsaturated esters from (*Z*)-2-fluoro-1-alkenyliodonium salts[a]

Entry	**1**	React. Time, h	Product	Yield, %[b]
1	 **1a**	2	 **2a**	73
2	 **1b**	2	 **2b**	70
3	 **1c**	0.5	 **2c**	64
4	 **1d**	2	 **2d**	67
5	 **1e**	2	 **2e**	66
6	 **1f**	2	 **2f**	68

a) The reaction was carried out as shown in an experimental part. b) Isolated yields based on alkyne used.

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(*Z*)-β-Fluoro-α,β-unsaturated esters can be stereoselectively prepared by the methoxycarbonylation of (*Z*)-2-fluoro-1-alkenyliodonium salts.