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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

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

(eq 1)

2. Results and discussion

The methoxycarbonylation reaction of (*Z*)-2-fluoro-1-dodecenyliodonium tetrafluoroborate (**1a**) was carried out using PdCl₂ as a catalyst and Et₃N 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 NaHCO₃ instead of Et₃N, 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 ^1H -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 (^1H , ^{13}C) and CFC_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 TeflonTM 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 °C. 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} . ^1H 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, $^3J_{\text{H-F}}=17.3$, $J=7.6$ Hz), 6.52 (d, 1H, $^3J_{\text{H-F(olefin)}}=33.2$ Hz), 7.45-8.02 (m, 5H). ^{19}F NMR δ -63.90 (d, $^3J_{\text{H-F(olefin)}}=33.2$ 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, $^2J_{\text{C-F}}=23.2$ Hz), 74.20 (d, $^2J_{\text{C-F}}=21.5$ Hz), 111.40, 132.28 (2C), 132.64, 135.27 (2C), 174.19 (d, $^1J_{\text{C-F}}=280.0$ Hz). Anal. calcd. for $\text{C}_{18}\text{H}_{27}\text{BF}_5\text{I}$; 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} . ^1H 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, $^3J_{\text{H-F}} = 17.3$, $J = 7.6$ Hz), 3.72 (s, 3H), 5.18 (d, 1H, $^3J_{\text{H-F(olefin)}} = 33.1$ Hz); ^{19}F NMR δ -79.53 (dt, 1F, $^3J_{\text{H-F}} = 17.3$, $^3J_{\text{H-F(olefin)}} = 33.1$ 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, $^2J_{\text{C-F}} = 24.1$ Hz), 51.33, 98.38 (d, $^2J_{\text{C-F}} = 6.0$ Hz), 164.30, 172.40 (d, $^1J_{\text{C-F}} = 281.1$ Hz). HRMS (EI) calc. for $\text{C}_{13}\text{H}_{22}\text{FO}$ (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} . ^1H NMR δ 3.80 (s, 3H), 5.92 (d, 1H, $^3J_{\text{H-F(olefin)}} = 33.4$ Hz), 7.42-7.68 (m, 5H). ^{19}F NMR δ -96.25 (d, $^3J_{\text{H-F(olefin)}} = 33.4$ Hz). ^{13}C NMR δ 51.59, 96.75 (d, $^2J_{\text{C-F}} = 7.4$ Hz), 125.61 (d, 2C, $^3J_{\text{C-F}} = 8.2$ Hz), 128.86 (2C), 130.51 (d, $^2J_{\text{C-F}} = 25.6$ Hz), 131.55, 164.48, 166.41 (d, $^1J_{\text{C-F}} = 277.6$ Hz). HRMS (EI): calc. for $\text{C}_{10}\text{H}_9\text{FO}_2$: 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} . ^1H NMR δ 0.91-1.00 (m, 2H), 1.09-1.31 (m, 3H), 1.59-1.77 (m, 6H), 2.14 (dd, 2H, $^3J_{\text{H-F}} = 20.9$, $J = 7.1$ Hz), 3.72 (s, 3H), 5.16 (d, 1H, $^3J_{\text{H-F(olefin)}} = 32.9$ Hz). ^{19}F NMR δ -78.63 (dt, $^3J_{\text{H-F}} = 20.9$, $^3J_{\text{H-F(olefin)}} = 32.9$ Hz). ^{13}C NMR δ 25.93 (2C), 26.09, 32.82 (2C), 34.87, 40.85 (d, $^2J_{\text{C-F}} = 23.1$ Hz), 51.27, 99.45 (d, $^2J_{\text{C-F}} = 5.7$ Hz), 164.18, 171.26 (d, $^1J_{\text{C-F}} = 286.6$ Hz). HRMS (EI): calc. for $\text{C}_{11}\text{H}_{17}\text{FO}_2$: 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} . ^1H NMR δ 1.30-1.44 (m, 10H), 1.52-1.60 (m, 2H), 1.73-1.80 (m, 2H), 2.27 (dt, 2H, $^3J_{\text{H-F}} = 17.3$, $J = 7.6$ Hz), 3.53 (t, 2H, $J = 6.8$ Hz), 3.72 (s, 3H), 5.18 (d, 1H, $^3J_{\text{H-F(olefin)}} = 33.1$ Hz). ^{19}F NMR δ -79.61 (dt, $^3J_{\text{H-F}} = 17.3$, $^3J_{\text{H-F(olefin)}} = 33.1$ Hz). ^{13}C NMR δ 25.50, 26.79, 28.70, 28.76, 29.05, 29.19, 32.57, 32.93 (d, $^2J_{\text{C-F}} = 23.1$ Hz), 45.10, 51.30, 98.42 (d, $^2J_{\text{C-F}} = 4.9$

Hz), 164.24, 172.29 (d, $^1J_{C-F} = 285.8$ 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} . 1H 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, $^3J_{H-F(olefin)} = 33.2$ Hz). ^{19}F NMR δ -79.60 (dt, $^3J_{H-F} = 17.7$, $^3J_{H-F(olefin)} = 33.2$ Hz). ^{13}C NMR δ 21.82 (2C), 24.92, 25.49, 28.68, 28.97 (2C), 29.00, 32.92 (d, $^2J_{C-F} = 23.9$ Hz), 34.63, 51.28, 67.32, 98.39 (d, $^2J_{C-F} = 5.7$ Hz), 164.24, 172.28 (d, $^1J_{C-F} = 286.6$ 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} . 1H NMR δ 1.10 (s, 9H), 1.20-1.32 (m, 8H), 1.47-1.56 (m, 4H), 2.23 (dt, 2H $^3J_{H-F} = 17.3$, $J = 7.8$ Hz), 2.43 (t, 2H, $J = 7.3$ Hz), 3.69 (s, 3H), 5.15 (d, 1H, $^3J_{H-F(olefin)} = 33.4$ Hz). ^{19}F NMR δ -79.59 (dt, $^3J_{H-F} = 17.3$, $^3J_{H-F(olefin)} = 33.4$ Hz). ^{13}C NMR δ 23.82, 25.50, 26.38 (3C), 28.70, 29.02, 29.18, 29.26, 32.92 (d, $^2J_{C-F} = 23.9$ Hz), 36.34, 44.06, 51.28, 98.39 (d, $^2J_{C-F} = 4.9$ Hz), 164.24, 172.33 (d, $^1J_{C-F} = 283.3$ Hz), 216.04. HRMS (EI): calc. for $C_{17}H_{29}FO_3$: 300.2101 found: 300.2109.

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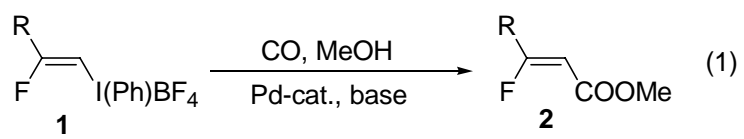
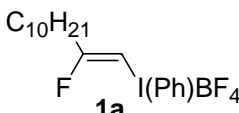
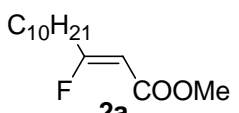
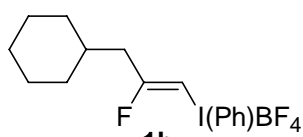
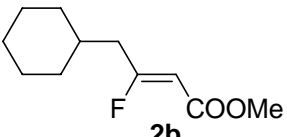
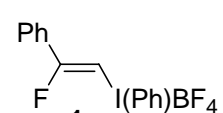
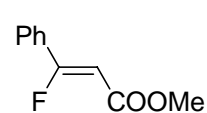
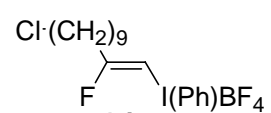
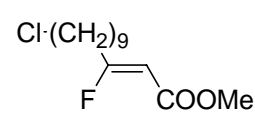
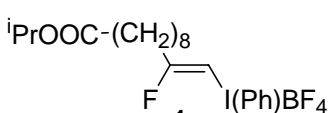
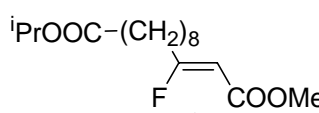
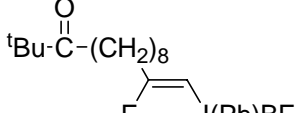
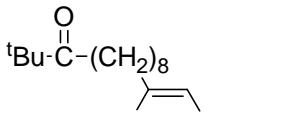


Table 1 Stereoselective synthesis of (*Z*)- β -fluoro- α,β -unsaturated esters from (*Z*)-2-fluoro-1-alkenyliodonium salts^a

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.

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

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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.

