Stereoselective synthesis of \((Z)\)-\(\beta\)-fluoro-\(\alpha,\beta\)-unsaturated esters from \((Z)\)-2-fluoro-1-alkenyliodonium salts

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Abstract

\((Z)\)-\(\beta\)-Fluoro-\(\alpha,\beta\)-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, \((Z)\)-\(\beta\)-fluoro-\(\alpha,\beta\)-unsaturated esters, Methoxycarbonylation reaction, Pd catalyst

1. Introduction

\(\alpha\)-Fluoro-\(\alpha,\beta\)-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 \(\beta\)-fluoro-\(\alpha,\beta\)-unsaturated esters [9]. Recently, we reported the stereoselective synthesis of \((E)\)-isomer of \(\beta\)-fluoro-\(\alpha,\beta\)-unsaturated esters by methoxycarbonylation of \((E)\)-2-fluoro-1-alkenyliodonium salts obtained from 1-alkynes and iodotoluene difluoride [10,11]. However, the stereoselective synthesis of the \((Z)\)-isomer of \(\beta\)-fluoro-\(\alpha,\beta\)-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 \(\beta\)-fluoro-\(\alpha,\beta\)-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$_3$N 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-tridecanoate (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$_3$N, 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, \(\delta\), 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 \(\mathbf{1}\) were prepared from the corresponding alkynes [13].

4.2. Preparation of (Z)-2-fluoro-1-dodecenyl(phenyl)iodonium tetrafluoroborate (\(\mathbf{1a}\)).

In a Teflon\textsuperscript{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 °C. The reaction mixture was poured into a 5% aqueous solution of NaBF\(_4\) (20 ml) and extracted with CH\(_2\)Cl\(_2\) (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\(_2\)Cl\(_2\)-hexane and dried in vacuo to give \(\mathbf{1a}\) in 84% yield (200 mg, 0.42 mmol): mp 27-28 °C. IR (KBr): \(\nu\) 3061, 3048, 2956 cm\(^{-1}\). \(^1\)H NMR \(\delta\) 0.88 (t, 3H, \(\textit{J}=7.3\) Hz), 1.19-1.31 (m, 14H), 1.52-1.60 (m, 2H), 2.57 (dt, 2H, \(\textit{J}_{\text{H-F}}=17.3, \textit{J}=7.6\) Hz), 6.52 (d, 1H, \(\textit{J}_{\text{H-F(olefin)}}=33.2\) Hz), 7.45-8.02 (m, 5H). \(^{19}\)F NMR \(\delta\) -63.90 (d, \(\textit{J}_{\text{H-F(olefin)}}=33.2\) Hz). \(^{13}\)C NMR \(\delta\) 14.11, 22.67, 25.48, 28.69, 29.03, 29.26, 29.35, 29.47, 31.86, 32.26 (d, \(\textit{J}_{\text{C,F}}=23.2\) Hz), 74.20 (d, \(\textit{J}_{\text{C,F}}=21.5\) Hz), 111.40, 132.28 (2C), 132.64, 135.27 (2C), 174.19 (d, \(\textit{J}_{\text{C,F}}=280.0\) Hz). Anal. calcd. for C\(_{18}\)H\(_{27}\)BF\(_4\)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 (\(\mathbf{2a}\)).

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 \(\mathbf{1a}\) (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$_4$Cl (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) $\nu$ 2926, 1735, 1685, 1217 cm$^{-1}$. $^1$H NMR $\delta$ 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$_{H-F}$ = 17.3, $J = 7.6$ Hz), 3.72 (s, 3H), 5.18 (d, 1H, $^3$J$_{H-F(olefin)}$ = 33.1 Hz); $^{19}$F NMR $\delta$ -79.53 (dt, 1F, $^3$J$_{H-F}$ = 17.3, $^3$J$_{H-F(olefin)}$ = 33.1 Hz). $^{13}$C NMR $\delta$ 14.11, 22.68, 25.54, 28.80, 29.21, 29.29, 29.42, 29.53, 31.88, 32.98 (d, $^2$J$_{C-F}$ = 21.4 Hz), 51.33, 98.38 (d, $^2$J$_{C-F}$ = 6.0 Hz), 164.30, 172.40 (d, $^1$J$_{C-F}$ = 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) $\nu$ 1726, 1662, 1166 cm$^{-1}$. $^1$H NMR $\delta$ 3.80 (s, 3H), 5.92 (d, 1H, $^3$J$_{H-F(olefin)}$ = 33.4 Hz), 7.42-7.68 (m, 5H). $^{19}$F NMR $\delta$ -96.25 (d, $^3$J$_{H-F(olefin)}$ = 33.4 Hz). $^{13}$C NMR $\delta$ 51.59, 96.75 (d, $^2$J$_{C-F}$ = 7.4 Hz), 125.61 (d, 2C, $^3$J$_{C-F}$ = 8.2 Hz), 128.86 (2C), 130.51 (d, $^2$J$_{C-F}$ = 25.6 Hz), 131.55, 164.48, 166.41 (d, $^1$J$_{C-F}$ = 277.6 Hz). HRMS (EI): calc. for C$_{10}$H$_{9}$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) $\nu$ 2926, 1732, 1683, 1218 cm$^{-1}$. $^1$H NMR $\delta$ 0.91-1.00 (m, 2H), 1.09-1.31 (m, 3H), 1.59-1.77 (m, 6H), 2.14 (dd, 2H, $^3$J$_{H-F}$ = 20.9, $J = 7.1$ Hz), 3.72 (s, 3H), 5.16 (d, 1H, $^3$J$_{H-F(olefin)}$ = 32.9 Hz). $^{19}$F NMR $\delta$ -76.83 (dt, $^3$J$_{H-F}$ = 20.9, $^3$J$_{H-F(olefin)}$ = 32.9 Hz). $^{13}$C NMR $\delta$ 25.93 (2C), 26.09, 32.82 (2C), 34.87, 40.85 (d, $^2$J$_{C-F}$ = 23.1 Hz), 51.27, 99.45 (d, $^2$J$_{C-F}$ = 5.7 Hz), 164.18, 171.26 (d, $^1$J$_{C-F}$ = 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) $\nu$ 2931, 1732, 1685, 1218 cm$^{-1}$. $^1$H NMR $\delta$ 1.30-1.44 (m, 10H), 1.52-1.60 (m, 2H), 1.73-1.80 (m, 2H), 2.27 (dt, 2H, $^3$J$_{H-F}$ = 17.3, $J = 7.6$ Hz), 3.53 (t, 2H, $J = 6.8$ Hz), 3.72 (s, 3H), 5.18 (d, 1H, $^3$J$_{H-F(olefin)}$ = 33.1 Hz). $^{19}$F NMR $\delta$ -79.61 (dt, $^3$J$_{H-F}$ = 17.3, $^3$J$_{H-F(olefin)}$ = 33.1 Hz). $^{13}$C NMR $\delta$ 25.50, 26.79, 28.70, 28.76, 29.05, 29.19, 32.57, 32.93 (d, $^2$J$_{C-F}$ = 23.1 Hz), 45.10, 51.30, 98.42 (d, $^2$J$_{C-F}$ = 4.9
Hz), 164.24, 172.29 (d, $J_{C-F} = 285.8$ 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) $\nu$ 2933, 1731, 1684, 1218 cm$^{-1}$. $^1$H NMR $\delta$ 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, $J_{H-F(olefin)} = 33.2$ Hz). $^{19}$F NMR $\delta$ -79.60 (dt, $J_{H-F} = 17.7$, $J_{H-F(olefin)} = 33.2$ Hz). $^{13}$C NMR $\delta$ 21.82 (2C), 24.92, 25.49, 28.68, 28.97 (2C), 29.00, 32.92 (d, $J_{C-F} = 23.9$ Hz), 34.63, 51.28, 67.32, 98.39 (d, $J_{C-F} = 5.7$ Hz), 164.24, 172.28 (d, $J_{C-F} = 286.6$ 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) $\nu$ 2932, 1734, 1704, 1685, 1219 cm$^{-1}$. $^1$H NMR $\delta$ 1.10 (s, 9H), 1.20-1.32 (m, 8H), 1.47-1.56 (m, 4H), 2.23 (dt, 2H $J_{H-F} = 17.3$, $J = 7.8$ Hz), 2.43 (t, 2H, $J = 7.3$ Hz), 3.69 (s, 3H), 5.15 (d, 1H, $J_{H-F(olefin)} = 33.4$ Hz). $^{19}$F NMR $\delta$ -79.59 (dt, $J_{H-F} = 17.3$, $J_{H-F(olefin)} = 33.4$ Hz). $^{13}$C NMR $\delta$ 23.82, 25.50, 26.38 (3C), 28.70, 29.02, 29.18, 29.26, 32.92 (d, $J_{C-F} = 23.9$ Hz), 36.34, 44.06, 51.28, 98.39 (d, $J_{C-F} = 4.9$ Hz), 164.24, 172.33 (d, $J_{C-F} = 283.3$ Hz), 216.04. HRMS (EI): calc. for C$_{17}$H$_{29}$FO$_3$: 300.2101 found: 300.2109.

References


R
\[
\begin{align*}
&\text{F} &\underline{(\text{Ph})\text{BF}_4} \\
&\text{1} &\text{CO, MeOH} \\
&\text{Pd-cat., base} \\
&\text{2} &\text{F} \\
&\text{R} &\text{COOMe}
\end{align*}
\]

(1)
Table 1  Stereoselective synthesis of (Z)-β-fluoro-α,β-unsaturated esters from (Z)-2-fluoro-1-alkenyliodonium salts\textsuperscript{a}

<table>
<thead>
<tr>
<th>Entry</th>
<th>React. Time, h</th>
<th>Product</th>
<th>Yield, %\textsuperscript{b}</th>
</tr>
</thead>
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<tr>
<td>1</td>
<td>C\textsubscript{10}H\textsubscript{21} F 1a</td>
<td>2</td>
<td>C\textsubscript{10}H\textsubscript{21} F 2a</td>
</tr>
<tr>
<td>2</td>
<td>Ph 1b</td>
<td>2</td>
<td>Ph 2b</td>
</tr>
<tr>
<td>3</td>
<td>F 1c</td>
<td>0.5</td>
<td>F 2c</td>
</tr>
<tr>
<td>4</td>
<td>(CH\textsubscript{2})\textsubscript{9} Cl 1d</td>
<td>2</td>
<td>(CH\textsubscript{2})\textsubscript{9} Cl 2d</td>
</tr>
<tr>
<td>5</td>
<td>iPrOOC-(CH\textsubscript{2})\textsubscript{8} 1e</td>
<td>2</td>
<td>iPrOOC-(CH\textsubscript{2})\textsubscript{8} 2e</td>
</tr>
<tr>
<td>6</td>
<td>tBu-C-(CH\textsubscript{2})\textsubscript{8} 1f</td>
<td>2</td>
<td>tBu-C-(CH\textsubscript{2})\textsubscript{8} 2f</td>
</tr>
</tbody>
</table>

\textsuperscript{a} The reaction was carried out as shown in an experimental part.  \textsuperscript{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.

\[
\begin{align*}
R & \xrightarrow{\text{CO, MeOH, Pd-cat., base}} R \\
\text{F} & \xrightarrow{\text{I(Ph)BF_4}} \text{F} \\
\text{C}=\text{O} & \xrightarrow{\text{MeO}} \text{COOMe}
\end{align*}
\]