An Efficient Stereoselective Synthesis of (E)-β-Fluoroalkenylidonium Salts

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Abstract: Stereoselective synthesis of (E)-β-fluoroalkenylidonium salts was performed by the treatment of alk-1-ynes with p-iodotoluene difluoride in the presence of HBF₄-Et₂O. The reaction occurred instantaneously at −78 °C to give the fluoroalkenylidonium salts in good yields with high stereoselectivity. The Pd-catalyzed carbomethoxylation of the fluoroalkenylidonium salt was also carried out to obtain a (E)-β-fluoro-α,β-unsaturated ester.

Key words: iodonium salt, fluoroalkene, p-iodotoluene difluoride, stereoselective synthesis, fluorination reaction

Fluorine-containing organic compounds are widely used in medicinal and agricultural chemicals, since the fluorinated analogue of a biologically active compound often shows greater bioactivity than the original compound. In a synthesis of a bioactive compound having a fluoroalkene moiety, the regio- and stereoselective introduction of the fluorine atom is important because the biological activity strongly depends on the position and stereochemistry of the fluorine atom. Therefore, much effort has been made for development of a regio- and stereospecific fluoroalkene synthesis. The most popular approach to the stereoselective synthesis of fluoroalkenes is via the Horner–Wadsworth–Emmons reaction using fluoride-containing organophosphonate; however, in this methodology, a mixture of stereoisomers is generally formed. Recently, Mestdagh et al. reported the stereoselective synthesis of (E)-2-fluoro-1-iodoalk-1-enes by iodofluorination of alk-1-ynes with bis(pyridinium)iodoni-um salt and pyridinium poly(hydrogen fluoride). Although they prepared only two simple fluoroiodoalkenes from hept-1-yne and phenylacetylene, they demonstrated the stereoselective fluoroalkene synthesis by the Pd-catalyzed cross-coupling reactions using the fluoroiodoalkenes. In our recent study, we reported that the reaction of alk-1-ynes with p-iodotoluene difluoride (I) in Et₃N–5HF proceeded at 0 °C to give (E)-β-fluoroalkenylidonium salts (2, X = F, Figure 1) stereoselectively. Moreover, the Pd-catalyzed cross-coupling reactions using the (E)-β-fluoroalkenylidonium salts smoothly occurred at room temperature to afford a variety of (E)-2-fluoroalk-1-ene derivatives stereoselectively. Since both the preparation of 2 (X = F) and its cross-coupling reactions can be carried out under mild reaction conditions, various functional groups are tolerated in the course of the fluoralkene synthesis. Thus, the fluoroalkenylidonium salt was found to be a good synthon for the stereoselective synthesis of fluoroalkenones; however, we have to handle a highly toxic reagent, anhydrous hydrogen fluoride, in the preparation of Et₃N–5HF, which was necessary for the synthesis of fluoroalkenylidonium salts. In this short paper, we present the preparation of 2 (X = BF₄) by the reaction of alk-1-ynes with 1 using HBF₄-Et₂O, which is a commercially available and relatively low toxic reagent. The Pd-catalyzed carbomethoxylation of 2 (X = BF₄) is also described.

Figure 1

Initially, a simple terminal alkyne, dodec-1-yn, was employed as the starting material (Scheme 1). To the CH₂Cl₂ solution of 1 was added HBF₄-Et₂O at −78 °C to give a deep green-colored reaction mixture. Then dodecyn was added to the reaction mixture at −78 °C, and the green color quickly changed into light yellow. The reaction completed in five minutes and dodecyn was transformed into (E)-β-fluorododec-1-enyl(4-methylphenyl)iodonium tetrafluoroborate (2a) in 74% yield with high stereoselectivity (E/Z > 98:2).

Scheme 1

A variety of alk-1-ynes were subjected to the reaction to synthesize (E)-β-fluoroalkenylidonium salts 2b–f as shown in Table 1. Although a little excess amount of 1 and HBF₄-Et₂O were required to consume the alkynes completely, various functional groups, e.g., AcO, Cl, COOMe and t-BuCO, are tolerated in the reactions (entries 1–4). Unfortunately, the terminal acetylene bearing an electron-withdrawing group adjacent to the triple bond was found to be inert in the reaction conditions (entry 6). In order to show the usefulness of the fluoroalkenylidonium salts, the Pd-catalyzed carbomethoxylation using 2a was performed (Scheme 2). The carbomethoxylation smoothly proceeded at room temperature in one hour to
give methyl (E)-3-fluorotridec-2-enoate (3a) in 91% yield with retention of the stereochemistry (E/Z > 98:2). It was found that the coupling reaction selectively took place at the alkenyl part of 2a, since only a trace amount of methyl 4-methylbenzoate (4a), which was formed by the carbomethoxylation of the 4-methylphenyl part in 2a, was detected after the reaction.

**Table 1** Stereoselective Synthesis of (E)-β-Fluoroalkenyliodonium Salts

<table>
<thead>
<tr>
<th>Entry</th>
<th>R Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AcO-(CH2)3</td>
<td>2b</td>
</tr>
<tr>
<td>2</td>
<td>CH-(CH2)3</td>
<td>2c</td>
</tr>
<tr>
<td>3</td>
<td>MeOOC-(CH2)3</td>
<td>2d</td>
</tr>
<tr>
<td>4</td>
<td>Bu-CO-(CH2)3</td>
<td>2e</td>
</tr>
<tr>
<td>5</td>
<td>Cl-(CH2)9</td>
<td>2f</td>
</tr>
<tr>
<td>6</td>
<td>EIOOC</td>
<td></td>
</tr>
</tbody>
</table>

* a Reactions were carried out on a 1 mmol scale unless noted otherwise using 1.3 equiv of I and 1.2 equiv of HBF4–Et2O.
* b Isolated yield based on alk-1-yne.
* c Reaction was carried out with 1.2 equiv of HBF4–Et2O.
* d No reaction.

In summary, the stereoselective synthesis of (E)-β-fluoroalkenyliodonium salts has been achieved by the addition of p-iodotoluene difluoride (I, 256 mg, 1.0 mmol) to the reaction mixture for 5 min at –78 °C, dodec-1-ynyl (166 mg, 1 mmol) was added to the reaction mixture and the whole reaction mixture was stirred for 5 min at –78 °C. The resulting solution was poured into 5% NaBF4 (20 mL) and extracted with CH2Cl2 (4 × 10 mL). The combined organic phase was dried over MgSO4 and concentrated under reduced pressure. The resulting viscous oil was dissolved in CH2Cl2 (1 mL) and a white suspension was formed by the addition of hexane (40 mL). A white suspension was left in a refrigerator for 2 h and clear upper liquid was removed by decantation. The remaining precipitate was washed with hexane (5 mL) again, separated from hexane by decantation. Finally, the solvate was removed in vacuo to give pure 2a (74%, 363 mg, 0.74 mmol, E/Z > 98:2); mp 69.7–70.5 °C.

**Scheme 2**

In summary, the stereoselective synthesis of (E)-β-fluoroalkenyliodonium salts has been achieved by the addition of p-iodotoluene difluoride to alk-1-ynes in the presence of HBF4–Et2O. The addition reaction completed instantaneously at –78 °C to give the fluoroalkenyliodonium salts in good yields.

IR spectra were recorded using a JASCO FT/IR-410 spectrometer. The 1H NMR (400 MHz), 19F NMR (376 MHz) and 13C NMR (100 MHz) spectra were recorded in CDCl3 on a JEOL JNM-A400II FT NMR spectrometer and the chemical shifts, δ, are referred to TMS (1H, 13C) and CFCl3 (19F). The Fab low- and high-resolution mass spectra were measured on a JEOL JMS-700TZ, JMS-FABmate or JMS-HX110 instrument. The melting points were measured with a Yanagimoto micro melting point apparatus and are uncorrected. Undec-10-ynoic acid (2b) and 3-cyclohexylprop-1-ynoic acid (2b) were prepared according to the literature. Methyl undec-10-ynoate was obtained by esterification of undec-10-ynoic acid (2b) prepared from undec-10-ynoic acid. 11-Acetoxyundec-1-yne (1d) and 11-chloroundec-1-yne (1b) were obtained from 11-hydroxyundec-1-ylene prepared from 11-hydroxyundec-1-ene. Undec-10-ynoic acid, 11-hydroxyundec-1-ene and propionic acid ethyl ester were purchased from Tokyo Kasei Co., Ltd., and used without further purification. HBF4–Et2O was purchased from Fluka Co., Ltd.

**Stereoselective Synthesis of (E)-β-Fluoroalkenyliodonium Salts; (E)-2-Fluorododec-1-enyl(4-methylphenyl)iodonium Tetrafluoroborate (2a); Typical Procedure**

To a CH2Cl2 solution (5 mL) of p-iodotoluene difluoride (I, 256 mg, 1.0 mmol) was added HBF4–Et2O (162 mg, 1.0 mmol) at –78 °C. After stirring the reaction mixture for 5 min at –78 °C, dodec-1-yne (166 mg, 1 mmol) was added to the reaction mixture and the whole reaction mixture was stirred for 5 min at –78 °C. The resulting solution was poured into 5% NaBF4 (20 mL) and extracted with CH2Cl2 (4 × 10 mL). The combined organic phase was dried over MgSO4 and concentrated under reduced pressure. The resulting viscos oil was dissolved in CH2Cl2 (1 mL) and a white suspension was formed by the addition of hexane (40 mL). A white suspension was left in a refrigerator for 2 h and clear upper liquid was removed by decantation. The remaining precipitate was washed with hexane (5 mL) again, separated from hexane by decantation. Finally, the solvate was removed in vacuo to give pure 2a (74%, 363 mg, 0.74 mmol, E/Z > 98:2); mp 69.7–70.5 °C.

**IR (KBr):** 3083, 2930, 2855, 1737, 1703, 1638, 1433, 1369, 1244, 1127, 1065, 802 cm–1.

**1H NMR:** δ = 0.88 (t, J = 7.1 Hz, 3 H), 2.12–2.29 (m, 14 H), 1.45–1.53 (m, 2 H), 2.41 (s, 3 H), 2.78 (dt, JH-F = 22.2 Hz, J = 7.6 Hz, 2 H), 6.70 [d, JH-F(olefin) = 14.4 Hz, 1 H], 7.26 (d, J = 8.3 Hz, 2 H), 7.84 (d, J = 8.5 Hz, 2 H).

**13C NMR:** δ = 14.09, 21.35, 22.65, 25.79, 28.90, 29.22, 29.27, 29.35, 29.47, 31.84, 32.13 (d, JCF = 23.1 Hz), 78.33 (d, JCF = 47.1 Hz), 108.19, 133.10 (2 × C), 134.60, 134.62, 143.76, 175.91 (d, JCF = 285.8 Hz).

**1F NMR:** δ = –66.71 [dt, JH-F = 22.2, JH-F(olefin) = 14.4 Hz, 1 F].

**MS:** m/z (%) = 403 (100) [M+ – BF4], 307 (31), 289 (16), 155 (20), 154 (82), 138 (22), 137 (41), 136 (54), 107 (17), 91 (15), 90 (12), 89 (20), 78 (11), 77 (22), 55 (16), 43 (11), 41 (17), 39 (18).


**Scheme 2**

In summary, the stereoselective synthesis of (E)-β-fluoroalkenyliodonium salts has been achieved by the addition of p-iodotoluene difluoride to alk-1-ynes in the presence of HBF4–Et2O. The addition reaction completed instantaneously at –78 °C to give the fluoroalkenyliodonium salts in good yields.

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**STEREOSELECTIVE SYNTHESIS OF (E)-รถยนาลากอนิเดียมสัลส์**

**SYNTHESIS OF (E)-3-FLUOROTRICARBOXYLIC ACID (3a)**

In a flask fitted with a balloon (3 L), were placed PdCl2 (1.8 mg, 0.01 mmol), NaHCO3 (42 mg, 0.65 mmol) and MeOH (4 mL). After the complete replacement of the atmosphere in the flask with CO, the reaction mixture was poured into 15% aq NH4Cl (15 mL) and extracted with Et2O (3 x 10 mL). The combined organic phase was dried over MgSO4 and concentrated under reduced pressure. Purification by column chromatography (silica gel/hexane–Et2O) gave 3a in 91% yield (99 mg, 0.46 mmol, E/Z > 98:2). For the spectrum information of 3a, see ref.3a.

**REFERENCES**


(9) The stereochemistry was determined by $^1$H NMR. A vinylic hydrogen of 2a appeared at 6.70 ppm as a doublet ($J_{HF} = 14.4$ Hz), which was in good agreement with the reported data of a (E)-fluoroalkenyliodonium salt; see ref. 7. A larger coupling constant ($J_{HF} = 33.2$ Hz) was observed from (Z)-2-fluorododecenyliodonium tetrafluoroborate: Yoshida, M.; Hara, S. Org. Lett. 2003, 5, 573.