Pergamon

Tetrahedron Letters 40 (1999) 7815–7818

TETRAHEDRON
LETTERS

Stereoselective synthesis of (*E*)-β-fluoro-α,β-unsaturated esters by carbonylation of (*E*)-2-fluoro-1-iodo-1-alkenyliodonium salts

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Received 14 July 1999; revised 16 August 1999; accepted 20 August 1999

Abstract

(*E*)-β-Fluoro-α,β-unsaturated esters were stereoselectively obtained by the palladium-catalyzed carbonylation reaction of (*E*)-2-fluoro-1-iodo-1-alkenyliodonium salts obtained by the addition of iodotoluene difluoride to 1-alkynes. © 1999 Elsevier Science Ltd. All rights reserved.

Key words: Carbonylation, fluorine and compounds, hypervalent elements

(*E*)-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[1] because they can be stereoselectively prepared by the Horner-Wadsworth-Emmons reaction using ethyl 2-fluorodiethylphosphonoacetate.[2] Though some other stereoselective methods for the fluorinated unsaturated carbonyl compounds have been reported,[3] a fluorine atom was always introduced into the α-position of the carbonyl group and the stereoselective synthesis of β-fluoro-α,β-unsaturated esters has not been reported.[4] In order to synthesize various kinds of analogs having a fluorine atom on their double bond, a new method for the stereoselective synthesis of β-fluoro-α,β-unsaturated esters has been required. Recently, we found that iodotoluene difluoride (1) adds to 1-alkynes to give (*E*)-2-fluoro-1-alkenyl-1-iodonium salts (2) stereoselectively.[5] We wish to report here that (*E*)-β-fluoro-α,β-unsaturated esters (3) can be prepared by the palladium-catalyzed carbonylation of 2 (eq. 1).

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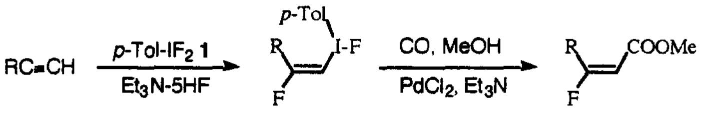
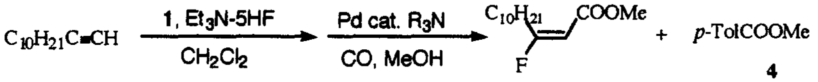
PII: S0040-4039(99)01626-3



2 3 (1)

The methoxycarbonylation reaction of alkenyliodonium salt **2** obtained from 1-dodecyne was examined under various reaction conditions (Table 1). Recently, the alkoxycarbonylation of 1,2-difluoro-1-iodoalkenes was reported to proceed under the conditions of high temperature and high CO pressure.[6] The methoxycarbonylation of 2-fluoro-1-dodecenyliodonium salt **2** proceeded at room temperature and under 1 atm of CO to provide methyl (*E*)-3-fluoro-2-tridecenoate stereoselectively (> 95 %)[7] with methyl 4-methylbenzoate (**4**) as a minor product.[8] The application of higher temperature (Entries 6 and 9) or higher CO pressures (Entry 5) was less effective. When the reaction was carried out in MeOH at room temperature under 1 atm of CO for 20 h using 0.1 mol% of $PdCl_2$ and 1 eq. of Et_3N to 1-dodecyne, the best result was obtained (Entry 7).

Table 1 Synthesis of Methyl (*E*)-3-Fluoro-2-tridecenoate[a]



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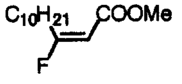
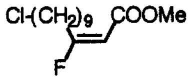
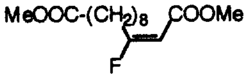
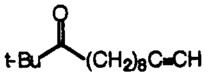
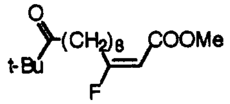
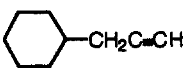
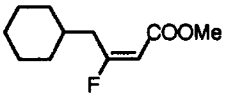
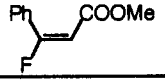
Entry	Catalyst, (mol%)	R_3N	React. temp.	Yield,%[b]
1	$Pd(OAc)_2$, (1)	Et_3N (1)	room temp.	54 (4)
2	$Pd(OAc)_2$, (5)	Et_3N (1)	room temp.	46 (4)
3	$Pd(OAc)_2$, (5)	Et_3N (3)	room temp.	28 (33)
4	$Pd(OAc)_2$, (5)	Bu_3N (1)	room temp.	44 (6)
5	$Pd(OAc)_2$, (5)	Et_3N (1)	room temp.	47(trace)[c]
6	$Pd(OAc)_2$, (5)	Et_3N (1)	50°C	45(5)
7	$PdCl_2$, (1)	Et_3N (1)	room temp.	58(3)
8	$PdCl_2$, (6)	Et_3N (1)	room temp.	50(12)
9	$PdCl_2$, (6)	Et_3N (1)	50°C	54(13)

[a] If otherwise not mentioned, the reaction was carried out under 1 atm of CO in 10 ml of MeOH for 20 h.
[b] Isolated yield based on 1-dodecyne, in parenthesis, the yield of methyl 4-methylbenzoate. [c] The reaction was carried out under 10 atm of CO.

Various kinds of 1-alkynes were used for the (*E*)-β-fluoro-α,β-unsaturated esters synthesis under the same reaction conditions (Table 2). The yields are not high because the alkenyliodonium salts **2**, prepared from 1-alkynes and **1**, were used for the methoxycarbonylation step without purification, and the overall yields of the two steps based on the 1-alkynes are shown. The alkynes having functional groups such as chloride (Entry 2), ketone (Entry 4), and ester (Entry 3) can be converted to the corresponding fluorinated unsaturated esters **3** without the protection of the functional groups. The isomeric purity of the products **3** was high (>95%) and only a small amount of methyl 4-methylbenzoate was formed (< 3%).

Table 2 Synthesis of (*E*)-β-Fluoro-α,β-unsaturated Esters[a]

Entry	Alkyne	Product	Yield, %[b]
1	$C_{10}H_{21}C{\equiv}CH$		58
2	$Cl\text{-}(CH_2)_9C{\equiv}CH$		66
3	$MeOOC\text{-}(CH_2)_8C{\equiv}CH$		60
4			51
5			57
6	Ph-C≡CH		57

[a] The reaction was carried out as shown in a text. [b] Isolation yields based on alkyne used.

A typical procedure is as follows. To a CH_2Cl_2 (3 ml) solution of 1-dodecyne (196 mg, 1 mmol) in a reaction vessel made of Teflon™ PFA, was added at 0 °C **1** (1.5 mmol) in Et_3N-5HF (11 ml).[9] After stirring for 2 h at 0 °C, the reaction was quenched by the addition of water (10 ml). The mixture was extracted with CH_2Cl_2, dried over $MgSO_4$, and concentrated under reduced pressure to give crude (*E*)-2-fluoro-1-dodecenyliodonium salt, which was used for the next step without purification. In a glass vessel fitted with a balloon (3 l), $PdCl_2$ (2 mg, 0.01 mmol) was placed and after replacing the atmosphere of the vessel with CO, the balloon was filled with CO. The crude iodonium salt **2** and Et_3N (101 mg, 1 mmol) in MeOH (10 ml) were then introduced into the reaction vessel. The reaction mixture was stirred at room temperature for 16 h and then poured into water. The product was extracted with ether and the combined organic phases were dried over $MgSO_4$. After concentration under reduced pressure, purification of the product by column chromatography (silica gel/hexane-ether) gave methyl (*E*)-3-fluoro-2-tridecenoate in 58% yield with a trace amount of methyl 4-methylbenzoate as a by-product. IR (neat): 1729, 1674 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.56 (d, *J* = 19.5 Hz, 1H), 3.71 (s, 3H), 2.80 (dt, *J* = 7.6, 25.6 Hz, 2H), 1.62-1.26 (m, 16H), 0.86 (t, *J* = 7.1 Hz, 3H); ^{19}F NMR (84.67

MHz, $CDCl_3/CCl_3F$) δ -75.43 - -76.26 (m, 1F); HRMS calcd for $C_{14}H_{25}O_2F$ 244.1839, Found 244.1841.

Acknowledgements

This work was financially supported by the Asahi Glass Foundation.

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8. As 4-iodotoluene was not converted to **4** under the reaction conditions, **4** was directly formed from **2**.
9. From 4-iodotoluene (327 mg, 1.5 mmol) and Et_3N-5HF (11 ml), **1** was prepared by the previously reported electrochemical method[5] and used as a Et_3N-5HF solution without purification.