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Stereo- and regioselective synthesis of (*E*,*E*)-δ-fluoro-α,β,γ,δ-unsaturated carbonyl compounds by Heck-type reaction of fluoroalkenyliodonium salts

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Abstract

(*E*,*E*)-δ-Fluoro-α,β,γ,δ-unsaturated carbonyl compounds were stereo- and regioselectively obtained by a palladium-catalyzed Heck-type reaction of (*E*)-2-fluoro-1-iodo-1-alkenyliodonium salts with α,β-unsaturated carbonyl compounds. The stereoselective synthesis of the fluorinated analogue of a biologically active unsaturated fatty acid was also achieved using this reaction.

Keywords: fluorine and compounds; Heck reactions; hypervalent elements.

The introduction of a fluorine atom into the double bond of natural products has been of great interest because the fluorinated analogues of natural compounds are expected to have pharmacological properties different from those of the original products.[1] Therefore, new methods for the stereoselective synthesis of fluoroalkenes have received considerable attention.[2]

Recently, we reported the stereo- and regioselective synthesis of (*E*)-(2-fluoro-1-alkenyl)(4-methylphenyl)iodonium fluorides (**2**) by the reaction of *p*-iodotoluene difluoride (**1**) with 1-alkynes[3] and its application to the stereoselective synthesis of β-fluoro-α,β-unsaturated esters.[4] We wish to report here that (*E*,*E*)-δ-fluoro-α,β,γ,δ-unsaturated carbonyl compounds (**3**) can be stereo- and regioselectively prepared by a palladium-catalyzed Heck-type olefination reaction of **2** with α,β-unsaturated carbonyl compounds (Scheme 1).

Moriarty et al. reported that the Heck-type olefination reaction of alkenyliodonium salts proceeds under mild conditions,[5] and we applied their reaction conditions to (*E*)-(2-fluoro-1-alkenyl)(4-methylphenyl)iodonium fluoride (**2**). A crude alkenyliodonium salt **2**, prepared by the reaction of *p*-iodotoluene difluoride (**1**) with 1-alkynes as previously reported,[3,4] was dissolved in DMF with an unsaturated carbonyl compound, $NaHCO_3$ and a catalytic amount of $Pd(OAc)_2$, and the mixture was stirred at room temperature for 16 h to give (*E*,*E*)-δ-fluoro-α,β,γ,δ-unsaturated carbonyl compounds

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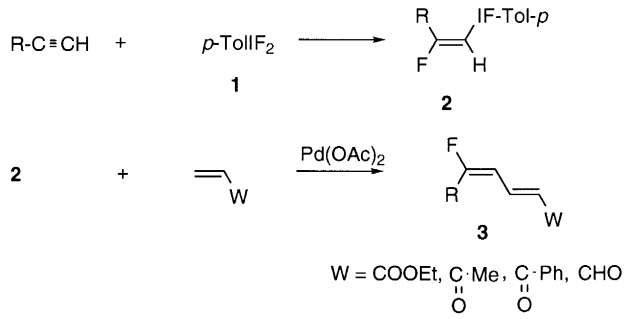

Scheme 1.

(**3**) stereoselectively [(*E*,*E*) >95%]. As unsaturated carbonyl compounds, the acrylic ester (**2a**), α,β-unsaturated ketones (**2b**,**c**), and acrolein (**2d**) were used and the corresponding fluorinated unsaturated carbonyl compounds were obtained as shown in Table 1. The functional groups such as the chloride (**1b**), ketone (**1c**) and ester (**1d**) in an alkyne can be tolerated under the reaction conditions, and consequently, the polyfunctional fluoroalkadienes can be directly prepared by our method.

Typical experimental procedure: To a CH_2Cl_2 (6 ml) solution of methyl 10-undecynoate (392 mg, 2 mmol) in a reaction vessel made of Teflon™ PFA was added at 0°C an Et_3N–5HF solution (22 ml) of *p*-iodotoluene difluoride prepared from *p*-iodotoluene (654 mg, 3 mmol).[3,4] After stirring for 8 h, the mixture was extracted with CH_2Cl_2, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was washed with hexane (10 ml) and the hexane layer was removed by decantation. The viscous residue was dissolved in DMF (10 ml) and then $NaHCO_3$ (504 mg, 6 mmol), $Pd(OAc)_2$ (31 mg, 0.14 mmol), and phenyl vinyl ketone (660 mg, 5 mmol) were added. The reaction mixture was stirred at room temperature for 2 h and then aqueous NH_4Cl was added. The product was extracted with ether and the combined organic layers were dried over $MgSO_4$. Purification by column chromatography (silica gel/hexane–ether) gave methyl (*E*,*E*)-10-fluoro-14-phenyl-14-oxo-10,12-tetradecadienoate in 68% yield. IR (neat): 1736, 1675 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J*=5.4 Hz, 2H), 7.58–7.46 (m, 4H), 6.99 (d, *J*=14.9 Hz, 1H), 6.02 (dd, *J*=11.9, 18.3 Hz, 1H), 3.66 (s, 3H), 2.52 (dt, *J*=7.6, 23.4 Hz, 2H), 2.30 (t, *J*=7.3 Hz, 2H), 1.58–1.61 (m, 4H), 1.31 (m, 8H); ^{19}F NMR (376 MHz, $CDCl_3/CCl_3F$) δ −85.34 (dt, *J*=18.3, 23.4 Hz, 1F); HRMS calcd for $C_{21}H_{27}O_3F$: 346.1937; found: 346.1966.

(9*Z*,11*E*)-13-Hydroxy-9,11-octadecadienoic acid (13 HODE) (**4**) shows interesting bioactivities[6] and its fluorinated analogues have attracted the attention of both chemists and biochemists.[7] We undertook the synthesis of the methyl ester of 9-fluoro 13 HODE (**5**) by our method. Methyl 9-decynoate (**6**) was reacted with **1** in the presence of Et_3N–5HF at room temperature and the resulting fluoroalkenyliodonium salt was used for the Heck-type reaction with 1-octen-3-one to give methyl (9*E*,11*E*)-9-fluoro-13-oxo-9,11-octadienoate (**7**) in 55% overall yield from **6**. The reduction of the keto-function of **7** provided the desired **5** quantitatively (Scheme 2).

Acknowledgements

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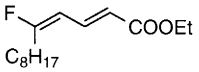
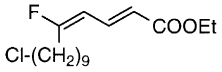
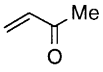
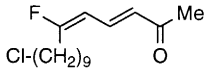
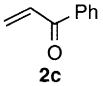
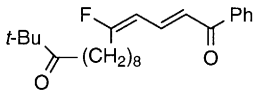
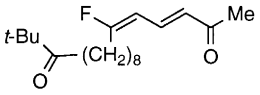
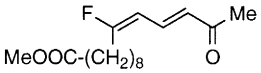
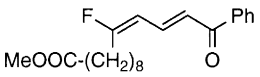
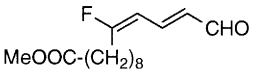
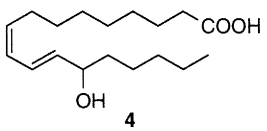
Table 1
Synthesis of (*E*,*E*)-δ-fluoro-α,β,γ,δ-unsaturated carbonyl compounds[a]

Entry	Alkyne	Alkene	Product[b]	Yield, %[c]
1	C_8H_{17}-C≡CH **1a**	COOEt **2a**		55
2	Cl-$(CH_2)_9$-C≡CH **1b**	**2a**		61
3	**1b**	 **2b**		65
4	*t*-Bu-CO-$(CH_2)_8$-C≡CH **1c**	 **2c**		66
5	**1c**	**2b**		61
6	MeOOC-$(CH_2)_8$-C≡CH **1d**	**2b**		60
7	**1d**	**2c**		68
8	**1d**	CHO **2d**		55

a) The reactions were carried out as shown in the text. b) Stereoselectivity of double bonds (*E*, *E*) > 95%.
c) Isolated yield based on alkyne used



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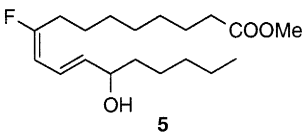

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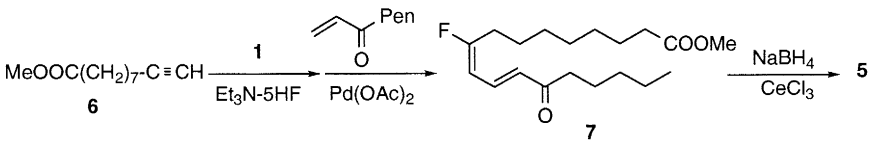

Scheme 2.

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