Stereo- and regio-selective addition of iodotoluene difluoride to alk-1-ynes. Selective synthesis of 2-fluoro-1-iodoalk-1-enes

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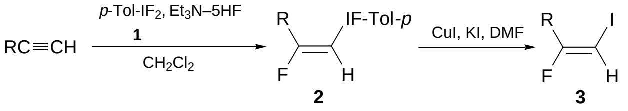
***p*-Iodotoluene difluoride reacted with 1-alkynes to give *trans* adducts which could be converted to 2-fluoro-1-iodoalk-1-enes without isolation.**

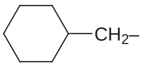
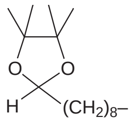
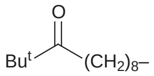
The introduction of a fluorine atom into the double bond of natural products, such as terpenes,[1] nucleosides,[2] retinal,[3] fatty acids,[4] prostaglandins[5] and peptides[6] has been of great interest because the fluorinated analogues of natural compounds are expected to have different pharmacological properties from the original ones. The fluoroalkenyl parts of such compounds have been synthesized by the condensation of α-fluorocarbanions with carbonyl compounds[3,5,6a,b,7] or the β-elimination reaction from fluorohaloalkanes[2,4b,6c] but the stereoselectivities are generally low. A cross-coupling reaction using fluoroalkenyl halides or fluoroalkenylmetals would be a versatile method for the stereoselective synthesis of fluoroalkenes.[8] However, the cross-coupling method has not been adequately developed for fluoroalkene synthesis because stereoselective synthesis of the fluoroalkenyl halides is difficult. Recently, we reported that *p*-iodotoluene difluoride (**1**) can be directly prepared from *p*-iodotoluene by an electrochemical method and used for the fluorination of β-dicarbonyl compounds.[9] During our continuing study of the organic synthesis using **1**, we found that **1** adds to alk-1-ynes to give (*E*)-(2-fluoroalk-1-enyl)(4-methylphenyl)iodonium fluorides (**2**)[10,11] which could be converted to (*E*)-2-fluoro-1-iodoalk-1-enes stereo- and regio-selectively (Scheme 1).



Scheme 1

p-Iodotoluene difluoride **1** was electrochemically prepared from *p*-iodotototoluene in Et$_3$N–5HF[9] and used for further reaction without isolation. (*E*)-(2-Fluoroalk-1-enyl)(4-methylphenyl)iodonium fluoride (**2**), which was stable and could be isolated and characterized, was used for the further transformation without isolation. The iodonation of **2** by modification of the reported procedure[12] provided (*E*)-2-fluoro-1-iodoalk-1-enes (**3**) in good yields (Table 1).‡ The reaction can be carried out without the protection of functionalities such as ketones, esters, and even hydroxy groups in alkynes. Further application of this method to the stereoselective synthesis of fluoroalkenes is under investigation.

Table 1 Synthesis of (*E*)-1-iodo-2-fluoroalk-1-enes[a]

Alkyne	R	Yield of **3** (%)[b]
a	Me(CH$_2$)$_9$–	80[c]
b	HO(CH$_2$)$_9$–	65[d]
c	Cl(CH$_2$)$_9$–	77[d]
d	MeO$_2$C(CH$_2$)$_8$–	80
e		65
f		55
g		72

[a] If not mentioned elsewhere, the reaction was carried out as described in the notes. [b] Isolated yields based on alkynes used. [c] After the reaction of alkyne with **1**, 1 equiv. of CuI and KI in DMF (2 ml) was added. [d] After the reaction of alkynes with **1**, the reaction mixture was added to 10 equiv. of CuI and KI in CH$_2$Cl$_2$ (30 ml).

Notes and References

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‡ *Typical experimental procedure*: *p*-iodotoluene difluoride was electrochemically prepared in a divided cell made of Teflon™ PFA with a Nafion™ 117 film using two smooth Pt Sheets (20 × 20 mm) for the anode and cathode. *p*-Iodotoluene (3 mmol) and Et$_3$N–5HF (22 ml) were introduced into the anodic cell and Et$_3$N–5HF (22 ml) was introduced into the cathodic cell. The electrolysis was carried out under constant electricity (50 mA h^{-1}) until 2 F mol^{-1} of electricity was passed. The resulting Et$_3$N–5HF solution of *p*-iodotoluene difluoride in the anodic cell was used for further reaction. Methyl undec-10-ynoate (293 mg, 2 mmol) and CH$_2$Cl$_2$ (6 ml) were introduced into a reaction vessel made of Teflon™ PFA and *p*-iodotoluene difluoride (3 mmol) in Et$_3$N–5HF (22 ml) was added at 0 °C. After stirring for 1 h, the mixture was extracted with CH$_2$Cl$_2$, dried over MgSO$_4$, and concentrated under reduced pressure. The residue was dissolved in CH$_2$Cl$_2$ (5 ml) and added to CuI (3.8 g, 20 mmol) and KI (3.32 g, 20 mmol) in CH$_2$Cl$_2$ (25 ml). The reaction mixture was stirred at room temperature for 3 h and extracted with CH$_2$Cl$_2$. The product was isolated by column chromatography (silica gel/hexane–diethyl ether) in 80% yield. C=C Stereochemistry of **3a–g** was determined from $^3J_{H-F}$ data. Stereospecificities of $>98\%$ are indicated by GC, and ^{1}H and ^{19}F NMR spectroscopy. *Spectral data* for **2a**: δ_H(400 MHz, CDCl$_3$) 7.866 (d, *J* 8.3, 2 H), 7.2015 (d, *J* 8.3, 2 H), 6.725 (d, *J* 15.125, 1 H), 2.662–2.754 (m, 2 H), 2.361 (s, 3 H). 1.167–1.576 (m, 14 H), 0.881 (t, 7.1, 3 H); δ_F(84.67 MHz, CDCl$_3$)(C$_6$F$_6$ as an internal standard) −69.131 to −69.834 (m, 1 F). For **3d**: δ_H(400 MHz, CDCl$_3$) 5.67 (d, *J* 17.81, 1 H), 3.67 (s, 3 H), 2.50 (dt, *J* 7.32, 22.4 Hz, 2 H), 2.31 (t, *J* 7.56, 2 H), 1.64–1.51 (m, 4 H), 1.35–1.31 (m, 8 H); δ_F(84.67 MHz, CDCl$_3$)(C$_6$F$_6$ as an internal standard) −81.969 to −82.721 (m, 1 F); ν(neat)/cm^{-1} 1735 and 1650.

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