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An efficient synthesis of fluorocyclopentenes using fluoroalkylidenecarbenes

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Abstract—An efficient synthesis of fluorocyclopentenes is described. By treatment of (2-fluoroalkenyl)iodonium salts with potassium *tert*-butoxide, (α-fluoroalkylidene)carbenes were generated efficiently to give fluorocyclopentenes via 1,5-C–H insertion. Fluorocyclopentenes having a functionality, such as chlorine, acetoxy, or ketone, and a spiro fluorocyclopentene were synthesized in good yields.

Fluoroalkene synthesis has received considerable attention from biological and medicinal chemists because the introduction of a fluorine atom into the double bond of a biologically active compound can dramatically enhance its bioactivity.[1,2] Therefore, much attention has been paid for the fluoroalkene synthesis, and many successful methodologies of terminal and internal fluoroalkene synthesis have been developed.[3,4] However, only a few methods for the synthesis of fluorocycloalkenes, especially fluorocyclopentenes, have been reported so far.[5–8] Since a cyclopentene moiety is a common structure in natural organic molecules, it would be worthwhile developing an efficient method for synthesizing fluorocyclopentenes to develop fluorinated pharmaceuticals. In 1993, Ochiai et al. reported that a fluorocyclopentene could be synthesized by 1,5-C–H insertion of an (α-fluoroalkylidene)carbene, which was generated by α-elimination of (*Z*)-(2-fluorohexadec-1-enyl)(phenyl)-iodonium tetrafluoroborate using tetrabutylammonium fluoride (TBAF) as a base. However, the fluorocyclopentene was obtained in only 17% yield and no other products were mentioned in their paper.[8] Moreover, there was no method for efficient synthesis of fluoroalkenyliodonium salts at that time.[9] Recently, we found that various (*Z*)-(2-fluoroalkenyl)iodonium salts **1** could be synthesized efficiently by the reaction of alkynyliodonium salts, which can be readily prepared from terminal alkynes,[10] with diluted aqueous HF.[11] In this context, we decided to investigate the synthesis of fluorocyclopentenes using **1**. First, we attempted to synthesize a fluorocyclopentene by the reaction of a fluoroalkenyliodonium salt with TBAF according to the reported procedure.[8] The results obtained by using (*Z*)-(11-acetoxy-2-fluoroundec-1-enyl)(phenyl)iodonium tetrafluoroborate (**1a**) as a starting material revealed that TBAF worked not only as a base but also as a fluoride source to afford a small amount of fluorocyclopentene, 3-(6-acetoxyhexyl)-1-fluorocyclopentene (**2a**, 9%), and a relatively large amount of 11-acetoxy-1,2,2-trifluoroundecane (**3**, 21%)[12] with many minor products (Scheme 1).[8,11,13]

We therefore investigated the reaction conditions to obtain a fluorocyclopentene efficiently using a simple fluoroalkenyliodonium salt, (*Z*)-(2-fluorododec-1-enyl)-(phenyl)iodonium tetrafluoroborate (**1b**), as a starting material (Table 1). A screening of bases showed that potassium *tert*-butoxide, *t*-BuOK, can dramatically increase the yield of fluorocyclopentene, and 3-heptyl-1-fluorocyclopentene (**2b**) was obtained in 66% yield (Table 1, entry 1). Other bases, including KOH (42%), NaOEt (39%), LDA (17%) and DBU (16%), gave lower yields than that obtained by using *t*-BuOK (Table 1, entries 2–5). The use of benzene, THF, and chlorobenzene as solvents gave **2b** in a range of 26–37% yields, and CH_2Cl_2 was found to be a good solvent for this reaction (Table 1, entries 1 and 6–8). Finally, the best result (**2b**, 74%) was obtained by the reaction of **1b** with *t*-BuOK (3 equiv) in CH_2Cl_2 at a low substrate concentration (0.01 M) (Table 1, entry 10).[14]

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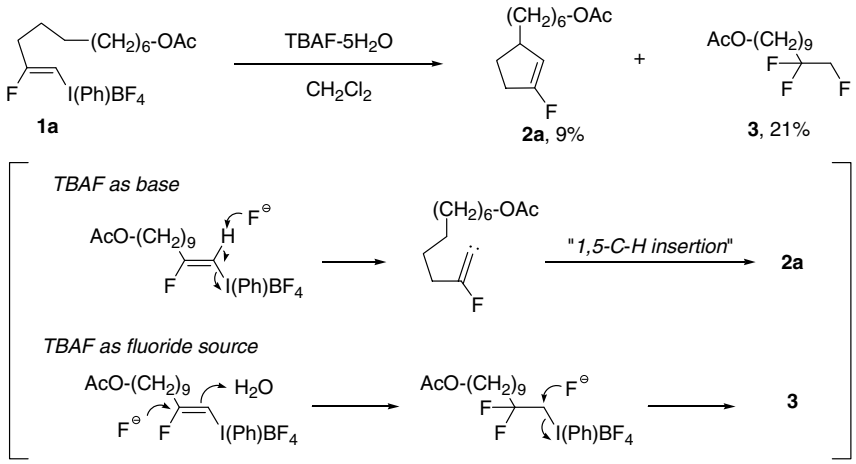
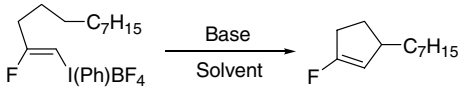


Scheme 1.

Table 1. Optimization of reaction conditions[a]



1b **2b**

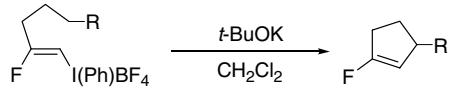
Entry	Base	Solvent	Yield[b] (%)
1	*t*-BuOK	CH_2Cl_2	66
2	KOH	CH_2Cl_2	42
3	NaOEt	CH_2Cl_2	39
4	LDA	CH_2Cl_2	17
5	DBU	CH_2Cl_2	16
6	*t*-BuOK	Benzene	27
7	*t*-BuOK	THF	26
8	*t*-BuOK	Chlorobenzene	37
9[c]	*t*-BuOK	CH_2Cl_2	70
10[d]	*t*-BuOK	CH_2Cl_2	74

[a] Unless otherwise mentioned, reactions were carried out with **1b** (0.5 mmol) and a base (0.75 mmol) in a solvent (10 mL, 0.05 M) at rt for 24 h.
[b] Isolated yield of **2b**.
[c] CH_2Cl_2 (50 mL, 0.01 M).
[d] Base (1.5 mmol), CH_2Cl_2 (50 mL, 0.01 M).

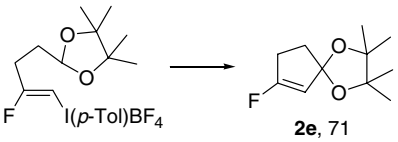
Under the same reaction conditions, the fluoroalkenyliodonium salt **1a** was also successfully converted into fluorocyclopentene **2a** in 68% yield, while the treatment of **1a** with TBAF gave only 9% yield as shown in Scheme 1 (Table 2, entry 1). Fluoroalkenyliodonium salts **1c** and **1d** having a functional group, for example, Cl or *t*-BuCO, could be converted into fluorocyclopentenes **2c** and **2d**, respectively, in good yields (Table 2, entries 2 and 3). The 1,5-C–H insertion of an (α-fluoroalkylidene)carbene into an acetal C–H bond also proceeded smoothly to afford a spiro product **2e** in 71% yield (Table 2, entry 4).

Next, we studied the effect of substituents of the aryliodanyl group of fluoroalkenyliodonium salts (Table 3, entries 1 and 2). (*Z*)-(2-Fluorododec-1-enyl)(*p*-tolyl)-iodonium tetrafluoroborate (**1f**) and (*Z*)-(2-fluorododec-1-enyl)(*p*-chlorophenyl)iodonium tetrafluoroborate (**1g**) were prepared and subjected to the reaction conditions.[11,15,16] By comparison with the reaction using **1b**,

Table 2. Synthesis of **2**[a]

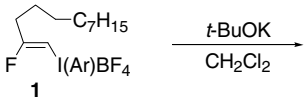


1 **2**

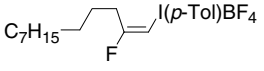
Entry	R	Yield[b] (%)
1	AcO-$(CH_2)_6$	**2a**, 68
2	Cl-$(CH_2)_6$	**2c**, 64
3	*t*-BuCO-$(CH_2)_5$	**2d**, 71
4		**2e**, 71

[a] Reagents and conditions: **1** (0.5 mmol), *t*-BuOK (1.5 mmol), CH_2Cl_2 (50 mL, 0.01 M), rt, 24 h.
[b] Isolated yield.

Table 3. Effect of substituents of the aryliodanyl group of fluoroalkenyl(aryl)iodonium salts on the synthesis of **2b**[a]



1

Entry	**1**	Yield[b] (%)
1	**1f**, Ar = *p*-Tol	74
2	**1g**, Ar = *p*-Cl–C_6H_4	70
3	 **1h, (*E*)-isomer of 1f**	76

[a] Reagents and conditions: **1** (0.5 mmol), *t*-BuOK (1.5 mmol), CH_2Cl_2 (50 mL, 0.01 M), rt, 24 h.
[b] Isolated yield.

it was found that neither the chlorine nor the methyl group has a significant influence on the yield of **2b** (74% from **1f** and 70% from **1g**) or on the reaction rate. In addition, the stereoisomer of **1f**, (*E*)-(2-fluorododec-1-enyl)(*p*-tolyl)iodonium tetrafluoroborate (**1h**),[17] also

gave **2b** in a similar yield (76%) under the same reaction conditions (Table 3, entry 3). These results indicate that the 1,5-C–H insertion occurred via an (α-fluoroalkylidene)carbene, not an (α-fluoroalkylidene)carbenoide, as in the reaction using the usual alkenyliodonium salts.[18]

In summary, we found that (α-fluoroalkylidene)carbenes can be generated efficiently by the reaction of (2-fluoroalkenyl)iodonium salts with potassium *tert*-butoxide in dichloromethane. The 1,5-C–H insertion of (α-fluoroalkylidene)carbenes smoothly proceeded to give fluorocyclopentenes having a functional group, for example, OAc, Cl, or *t*-BuCO, in good yields. A spiro fluorocyclopentene was also obtained by the 1,5-C–H insertion of a fluoroalkylidenecarbene into an acetal C–H bond.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.11.019.

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12. Compound **3** was obtained as a mixture with a small amount of impurities. Therefore, the yield of **3** was determined by ^{1}H NMR using an internal standard. For spectral data of a 1,2,2-trifluoroalkane, see Ref. 11.
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14. *Experimental procedure and spectra data for the synthesis of* **2b**: In a round-bottomed flask were placed (*Z*)-(2-fluorododec-1-enyl)(phenyl)iodonium tetrafluoroborate (**1b**) (238 mg, 0.5 mmol), CH_2Cl_2 (50 mL), and potassium *tert*-butoxide (168 mg, 1.5 mmol) at room temperature, and the mixture was stirred for 24 h at room temperature. The reaction mixture was poured into a satd aq NH_4Cl (30 mL) and the organic phase was separated. The aqueous phase was extracted with Et_2O (20 mL) three times. The combined organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The product, 1-fluoro-3-heptylcyclopentene (**2b**), was isolated by column chromatography (silicagel; hexane) in 74% yield (68 mg, 0.37 mmol); δ_H ($CDCl_3$) 0.88 (3H, t, *J* 6.7 Hz), 1.22–1.56 (13H, m), 2.08–2.15 (1H, m), 2.36–2.44 (2H, m), 2.54–2.64

(1H, m), 4.94–4.98 (1H, m); δ_F ($CDCl_3$) −122.2 (1F, s); δ_C ($CDCl_3$) 14.1, 22.7, 27.4, 27.7 (d, *J* 7.7 Hz), 28.6 (d, *J* 21.8 Hz), 29.3, 29.8, 31.9, 36.9 (d, *J* 1.9 Hz), 40.0 (d, *J* 7.7 Hz), 106.5 (d, *J* 8.6 Hz), 162.0 (d, *J* 278.8 Hz); *v* (KBr)/cm^{-1} 2954, 2925, 2855, 1679, 1460, 1350, 1164, 821, 723; [HR EI-MS: calcd for $C_{12}H_{21}F$ (M): 184.1627. Found: M^+, 184.1629].

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