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Fluorination of Ketones Using Iodotoluene Difluoride

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Abstract: Fluorination of ketones was achieved by the reaction of silyl enol ethers with iodotoluene difluoride in the presence of $\text{BF}_3 \cdot \text{OEt}_2$ and a $\text{Et}_3\text{N} \cdot \text{HF}$ complex.

Key words: fluorination, iodotoluene difluoride, silyl enol ether, ketone, hypervalent iodine

Introduction of a fluorine atom into the α -position of carbonyl compounds is the most effective method for the synthesis of α -fluorinated carbonyl compounds which have been used as important synthons in the preparation of more complex fluorine compounds.^{1,2} Though electrophilic fluorination reagents such as *N*-fluoro reagents have been used for their synthesis,³ dangerous F_2 is necessary for their preparation, and such reagents are expensive even if they are commercially available. Recently we reported that the direct fluorination reaction of β -dicarbonyl compounds can be achieved using iodotoluene difluoride (ITDF)^{4,5} which can be prepared in large quantity without F_2 .^{6,7} However, application of ITDF is restricted to β -dicarbonyl compounds^{4,5} or α -sulfanylated carbonyl compounds,⁸⁻¹¹ and ITDF is inert to monocarbonyl compounds. Previously, Tsushima et al. applied ITDF for the reaction with silyl enol ethers of steroidal ketones for the synthesis of steroidal fluoroketones.¹² However, olefinic by-products were competitively formed and yields of the desired α -fluoro ketones were low. During our continuous study of fluorination of carbonyl compounds using ITDF, we succeeded in improving the yield of fluorinated carbonyl compounds in the reaction of ITDF with silyl enol ethers.

When a silyl enol ether of acetophenone (**1a**) was allowed to react with ITDF at room temperature, it took 3 hours until the complete consumption of **1a**, and acetophenone and its dimmer (**5a**) were obtained as main products. Under the conditions, the formation of an iodonium salt (**2a**), which must be a key intermediate for the fluorinated product (**3a**),¹² seems to be slow and the generated iodonium salt **2a** decomposed to acetophenone or reacted with the remaining **1a** to give **5a** (Scheme 1). Zhadnkin et al. reported that the iodonium salts can be stably prepared at lower temperature by the reaction of **1** with an iodoarene difluoride- $\text{BF}_3 \cdot \text{OEt}_2$ complex.¹³ In order to make **2a** at low temperature, $\text{BF}_3 \cdot \text{OEt}_2$ was used with ITDF, and various fluoride

sources were applied to accelerate the fluorination of **2a** (Table 1). Though **1a** was consumed at $-78\text{ }^{\circ}\text{C}$ in the presence of $\text{BF}_3\cdot\text{OEt}_2$, the addition of metal fluorides such as KF and CsF , which are only slightly soluble in an organic solvent, failed to improve the yields of **3a**. On the other hand, the addition of $\text{Et}_3\text{N}\cdot\text{HF}$ complexes ($\text{Et}_3\text{N}\cdot n\text{HF}$) could improve the results. When a commercially available $\text{Et}_3\text{N}\cdot 3\text{HF}$ ^{14,15} was used as the fluoride source, **3a** could be obtained in 71% yield with a little amount of **4a** (9%) and **5a** (4%). $\text{Et}_3\text{N}\cdot 2\text{HF}$ could slightly improve the result but $\text{Et}_3\text{N}\cdot\text{HF}$, TBAF, and Et_4NF were less effective than $\text{Et}_3\text{N}\cdot 2\text{HF}$ or $\text{Et}_3\text{N}\cdot 3\text{HF}$.

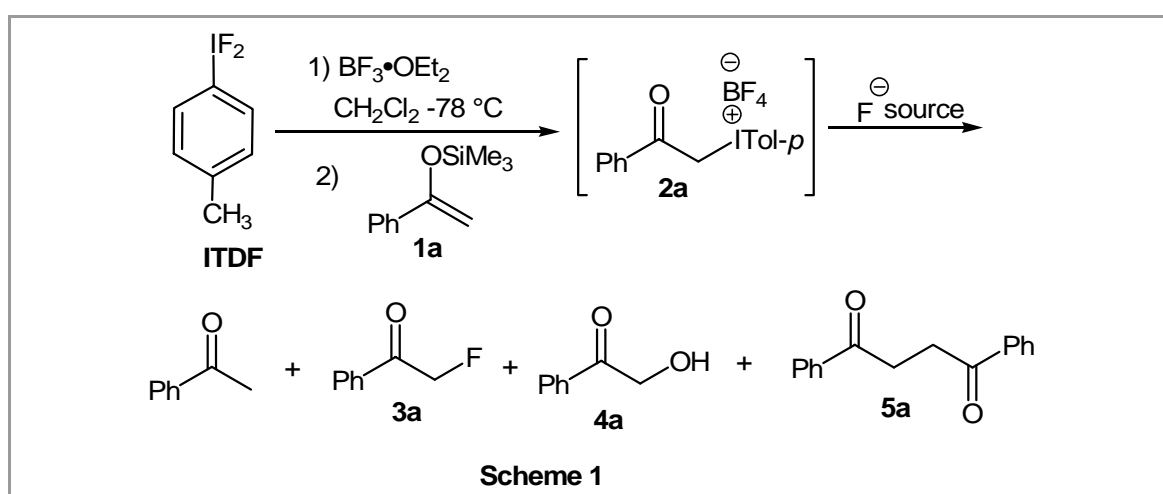


Table 1 Effect of Fluoride source on the Fluorination of **1a**^a

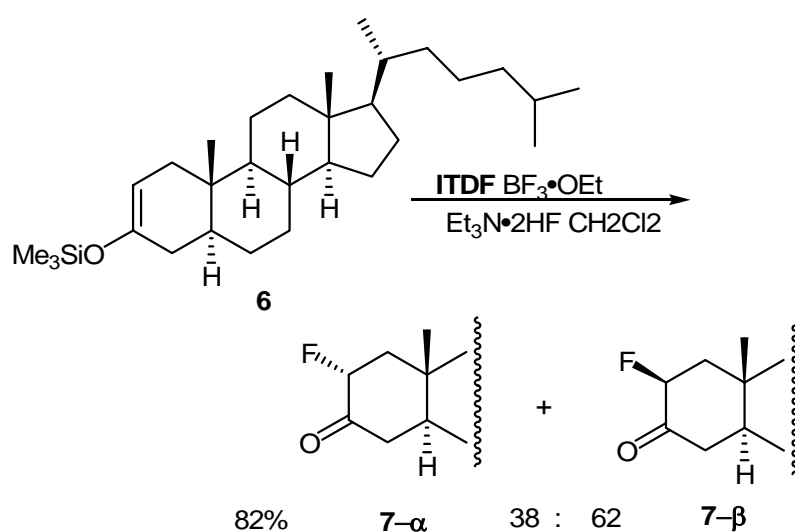
Fluoride source	Yield (%) ^b		
	3a	4a	5a
$\text{Et}_3\text{N}\cdot 3\text{HF}$	71	9	4
$\text{Et}_3\text{N}\cdot 2\text{HF}$	73	7	4
$\text{Et}_3\text{N}\cdot\text{HF}$	40	—	10
TBAF	25	9	3
Et_4NF	1	49	8
CsF^c	—	80	4
KF^c	10	75	5

^a If otherwise not mentioned, CH_2Cl_2 was used as solvent.

^b NMR yield based on **1a**. ^c CH_3CN was used as solvent.

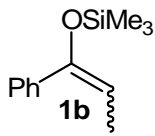
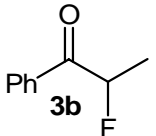
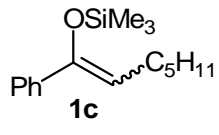
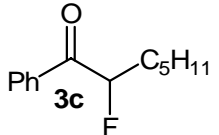
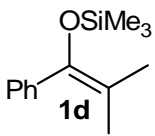
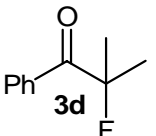
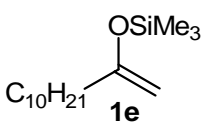
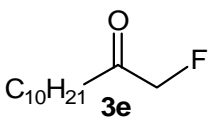
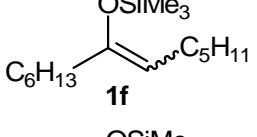
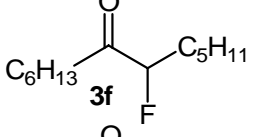
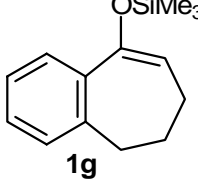
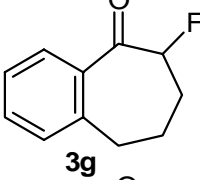
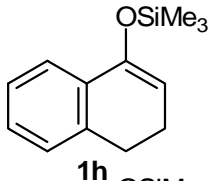
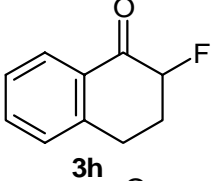
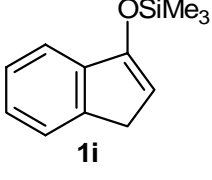
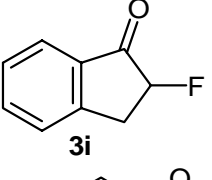
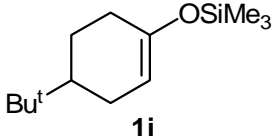
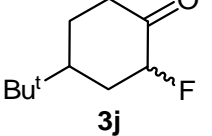
Under the conditions, silyl enol ethers of various acyclic and cyclic ketones could be converted to the corresponding α -fluoroketones (**3**) (Table 2).

Introduction of a fluorine atom to methyl (entry 4), methylene (entries 1,2,5-9), and even methyne carbon (entry 3) was also possible. When cyclic ketone silyl enol ethers were used (entries 6-9), the formation of an olefinic by-product was observed to an extent of <5 %. Fluorinated analogs of steroids have been of great interest for the study of their metabolic mechanism, and 2-fluorocolesterols were synthesized from their enol esters by the reaction with electrophilic fluorinating reagents. However, the products obtained by these methods are always α -isomers which are more favorable both kinetically and thermodynamically, and it was difficult to synthesize the β -isomers.¹⁶⁻¹⁸ On the other hand, when silyl enol ether of cholestan-3-one (**6**) was treated with ITDF, the β -isomer of 2-fluorocolestan-3-one (**7- β**) was obtained as a main product (Scheme 2). This unusual stereoselectivity can be explained by the formation of the iodonium intermediate.¹² ITDF attacks **6** from the less hindered α -face to give the α -isomer of the iodonium intermediate which reacts with a fluoride ion with inversion of stereochemistry to give the **7- β** .¹⁹



Scheme 2

Table 2 Reaction of Silyl Enol Ethers **1** with ITDF^a

Entry	Silyl Enol Ether 1	Product 3	Yield (%) ^b
1	 1b	 3b	60
2	 1c	 3c	82
3	 1d	 3d	66
4	 1e	 3e	70
5	 1f	 3f	85
6	 1g	 3g	62
7	 1h	 3h	60
8	 1i	 3i	50
9	 1j	 3j	61 ^c

^a The reactions were carried out in CH₂Cl₂ using ITDF, BF₃•OEt₂, and Et₃N•2HF to **1**. ^b Isolated yields based on **1** and yields of olefinic by-products were less than 5%. ^c Ratio of *cis* : *trans* = 1 : 1

The IR spectra were recorded using a JASCO FT/IR-410. The ^1H NMR (400MHz), ^{19}F NMR (376MHz), and ^{13}C NMR (100 MHz) spectra were recorded in CDCl_3 on a JEOL JNM-A400II FT NMR and the chemical shift, δ , are referred to TMS (^1H , ^{13}C) and CFCl_3 (^{19}F), respectively. The EI-high-resolution mass spectra were measured on a JEOL JMS-700TZ, JMS-FABmate or JMS-HX110. Melting points are measured by Yanagimoto micro melting point apparatus and are uncorrected.

ITDF was prepared from iodotoluene as reported previously.⁷ $\text{BF}_3\cdot\text{OEt}_2$ and $\text{Et}_3\text{N}\cdot 3\text{HF}$ were purchased from Tokyo Kasei Co., Ltd., and distilled under N_2 before use. $\text{Et}_3\text{N}\cdot 2\text{HF}$ and $\text{Et}_3\text{N}\cdot \text{HF}$ were prepared by the addition of freshly distilled Et_3N to $\text{Et}_3\text{N}\cdot 3\text{HF}$. The silyl enol esters **1** were prepared from the corresponding ketones according to a literature.²⁰ Ketones were obtained from Tokyo Kasei Co., Ltd., and used without purification.

Fluorination of Ketones **1** with Iodotoluene Difluoride; General Procedure

To a CH_2Cl_2 solution (10 mL) of ITDF (256 mg, 1.0 mmol) in Teflon FEP vessel²¹ were added at $-78\text{ }^\circ\text{C}$, $\text{BF}_3\cdot\text{OEt}_2$ (142 mg, 1.0 mmol), and after 10 min, silyl enol ether **1** (1.0 mmol). The reaction mixture was stirred at $-78\text{ }^\circ\text{C}$ for 2 h and a CH_2Cl_2 solution (5 mL) of $\text{Et}_3\text{N}\cdot 2\text{HF}$ (706 mg, 5.0 mmol) was added. After 1 h, the mixture was poured into water and the separated aqueous layer was extracted with CH_2Cl_2 (2X10mL). The combined organic layers were dried over MgSO_4 and product **3** was obtained by column chromatography (silica gel/hexane- Et_2O).

2-Fluoroacetophenone (**3a**)

IR (neat): 2992, 1700, 1598, 1450, 1233, 1132 cm^{-1} .

^1H NMR δ = 5.55 (d, $J_{\text{H-F}}$ = 46.8 Hz, 2H), 7.26-7.53 (m, 2H), 7.62-7.66 (m, 1H), 7.89-7.94 (m, 2H).

^{19}F NMR δ = -231.4 (t, $J_{\text{H-F}}$ = 46.8 Hz, 1F) [lit.²² -230.3 (t, J = 47 Hz)].

2-Fluoro-1-phenyl-1-propanone (**3b**)

IR (neat): 2955, 2932, 2860, 1699, 1597, 1449 cm^{-1} .

^1H NMR: δ = 1.64 (dm, $J_{\text{H-F}}$ = 38.6 Hz, 3H), 5.70 (dq, $J_{\text{H-F}}$ = 48.8, $J_{\text{H-H}}$ = 5.6 Hz, 1H), 7.48-7.52 (m, 2H), 7.60-7.64 (m, 1H), 7.96-7.99 (m, 2H).

^{19}F NMR: δ = -181.95 to -182.27 (m, 1F) (lit.²² -180.5).

2-Fluoro-1-phenyl-1-heptanone (**3c**)

IR (neat): 2955, 2932, 2860, 1699, 1597, 1449 cm^{-1} .

^1H NMR: δ = 0.89 (t, $J_{\text{H-H}}$ = 7.3 Hz, 3H), 1.30-1.38 (m, 4H), 1.50-1.57 (m, 2H), 1.90-2.02 (m, 2H), 5.57 (dm, $J_{\text{H-F}}$ = 49.5 Hz, 1H), 7.47-7.97 (m, 5H).

^{19}F NMR: δ = -190.54 - -190.27 (m, 1F).

^{13}C NMR: δ = 14.01, 22.47, 24.54 (d, $J_{\text{C-F}}$ = 3.3 Hz), 31.41, 32.83 (d, $J_{\text{C-F}}$ = 20.7 Hz), 93.97 (d, $J_{\text{C-F}}$ = 182.8 Hz), 128.80 (2C), 128.91 (d, $J_{\text{C-F}}$ = 3.3 Hz), 133.78 (2C), 134.42, 197.03 (d, $J_{\text{C-F}}$ = 19.8 Hz).

HRMS (EI): m/z calcd for $\text{C}_{13}\text{H}_{17}\text{OF}$: 208.1250; found: 208.1257.

2-Fluoro-2-methyl-1-phenyl-1-propanone (**3d**)

IR (neat): 2988, 1685, 1179 cm^{-1} .

^1H NMR: δ = 1.70 (d, $J_{\text{H-F}}$ = 21.5 Hz, 6H), 7.44-7.48 (m, 2H), 7.55-7.58 (m, 1H), 8.06-8.08 (m, 2H).

^{19}F NMR: δ = -144.32 to -143.98 (m, 1F) (lit.²² -142.1).

1-Fluoro-2-dodecanone (**3e**)

IR (neat): 2925, 2855, 1728, 1465, 1047.

^1H NMR: δ = 0.88 (t, $J_{\text{H,F}} = 7.0$ Hz, 3H), 1.26-1.30 (m, 14H), 1.56-1.65 (m, 2H), 2.54 (td, $J_{\text{H,H}} = 7.4$, $J_{\text{H,F}} = 2.9$ Hz, 2H), 4.80 (d, $J_{\text{H,F}} = 47.8$ Hz, 2H).

^{19}F NMR: δ = -228.01 (t, $J_{\text{H,F}} = 47.8$ Hz, 1F).

^{13}C NMR: δ = 14.12, 22.69, 22.76, 29.15, 29.31, 29.35, 29.45, 29.55, 31.90, 38.31, 84.97 (d, $J_{\text{C,F}} = 184.4$ Hz), 207.29 (d, $J_{\text{C,F}} = 19.0$ Hz).

HRMS (EI): m/z calcd for $\text{C}_{12}\text{H}_{23}\text{FO}$: 202.1741; found: 202.1737.

6-Fluoro-7-tridecanone (3f)

IR (neat): 2956, 2932, 1699, 1597, 1449 cm^{-1} .

^1H NMR: δ = 0.87-0.91 (m, 6H), 1.28-1.37 (m, 10H), 1.40-1.48 (m, 2H), 1.54-1.61 (m, 2H), 1.70-1.86 (m, 2H), 2.53-2.64 (m, 2H), 4.71 (dm, $J_{\text{H,F}} = 50.4$ Hz, 1H).

^{19}F NMR: δ = -192.64 to -192.35 (m, 1F).

^{13}C NMR: δ = 13.97, 14.03, 22.44 (d, $J_{\text{C,F}} = 10.8$ Hz), 22.64, 24.21 (d, $J_{\text{C,F}} = 2.5$ Hz), 28.84, 31.34, 31.58, 31.93, 32.14, 38.04, 96.09 (d, $J_{\text{C,F}} = 183.6$ Hz), 210.54 (d, $J_{\text{C,F}} = 24.8$ Hz).

HRMS (EI): m/z calcd for $\text{C}_{13}\text{H}_{25}\text{OF}$: 216.1890; found: 216.1890.

6-Fluoro-6,7,8,9-tetrahydrobenzocyclohepten-5-one (3g)

IR (neat): 2943, 1696, 1599, 1449 cm^{-1} .

^1H NMR: δ = 1.89-2.19 (m, 3H), 2.29-2.43 (m, 1H), 2.92-3.08 (m, 2H), 5.24 (dm, $J_{\text{H,F}} = 48.8$ Hz, 1H), 7.22-7.26 (m, 1H), 7.31-7.35 (m, 1H), 7.42-7.46 (m, 1H), 7.77 (d, $J_{\text{H,F}} = 7.8$ Hz, 1H).

^{19}F NMR: δ = -183.3 to -183.15 (m, 1F) (lit.²³ -183).

2-Fluoro-1-tetralone (3h)

White solid; Mp 34 °C (lit.²³ 38-40 °C).

IR (KBr): 2938, 2898, 1707, 1602, 1271, 1227 cm^{-1} .

^1H NMR: δ = 2.31-2.43 (m, 1H), 2.55-2.63 (m, 1H), 3.13-3.16 (m, 2H), 5.14 (dm, $J_{\text{H,F}} = 48.1$ Hz, 1H), 7.26-7.55 (m, 3H), 8.08 (d, $J_{\text{H,F}} = 7.8$ Hz, 1H).

^{19}F NMR: δ = -190.99 (dm, $J_{\text{H,F}} = 48.2$, 1F) [(lit.²³ -192 (dm, $J_{\text{H,F}} = 47.5$ Hz)].

2-Fluoroindan-1-one (3i)

White solid; Mp 56-58 °C (lit.²³ 54-56 °C).

IR (KBr): 2924, 1719, 1607, 1465, 1087 cm^{-1} .

^1H NMR: δ = 3.19-3.30 (m, 1H), 3.60-3.68 (m, 1H), 5.27 (dm, $J_{\text{H,F}} = 51.0$ Hz, 1H), 7.43-7.48 (m, 2H), 7.66-7.70 (m, 1H), 7.81 (d, $J = 7.6$ Hz, 1H).

^{19}F NMR: δ = -194.17 (ddd, $J_{\text{H,F}} = 51.0, 23.2, 7.4$ Hz, 1F) [(lit.²³ -192.5 (ddd, $J_{\text{H,F}} = 50, 22.5, 9$ Hz)].

cis-2-Fluoro-4-tert-butylcyclohexanone (cis-3j)

White solid; Mp 37 °C (lit.¹⁶ 40 °C).

IR (KBr): 2962, 1737, 1368 cm^{-1} .

^1H NMR: δ = 0.95 (s, 9H), 1.39-1.50 (m, 1H), 1.54-1.69 (m, 2H), 2.07-2.18 (m, 1H), 2.28-2.37 (m, 1H), 2.49-2.56 (m, 2H), 4.93 (dm, $J_{\text{H,F}} = 48.5$ Hz, 1H).

^{19}F NMR: δ = -188.62 (dm, $J_{\text{H,F}} = 48.2$ Hz, 1F).

***trans*-2-Fluoro-4-*tert*-butylcyclohexanone (*trans*-3j)**

White solid; Mp 69-71 °C (lit.¹⁶ 74 °C).

IR (KBr): 2956, 2871, 1722, 1365 cm⁻¹.

¹H NMR: δ = 0.92 (s, 9H), 1.42-1.70 (m, 2H), 1.84-1.92 (m, 1H), 2.10-2.19 (m, 1H), 2.35-2.45 (m, 2H), 2.76-2.86 (m, 1H), 4.67 (dm, *J*_{H,F} = 46.8 Hz, 1H).

¹⁹F NMR: δ = -186.28 to -185.98 (m, 1F).

2α-Fluorocholestan-3-one (7-α)

White solid. Mp 161-163 °C (lit.¹⁷ 168-169 °C)

IR (KBr): 2939, 2865, 1735, 1467, 1382 cm⁻¹.

¹H NMR: δ = 0.85-2.03 (m, 41H), 2.21-2.53 (m, 3H), 4.98 (dm, *J*_{H,F} = 48.1 Hz, 1H).

¹⁹F NMR: δ = -194.67 (dm, *J*_{H,F} = 48.1 Hz, 1F) (lit.¹⁷ -194.48).

2β-Fluorocholestan-3-one (7-β)

White solid; Mp 85-87 °C.

IR (KBr): 2932, 2861, 1735, 1467, 1382 cm⁻¹.

¹H NMR: δ = 0.85-1.87 (m, 40H), 1.97-2.02 (m, 1H), 2.16-2.26 (m, 2H), 2.59-2.68 (m, 1H), 4.79 (dt, *J*_{H,F} = 49.8, *J*_{H,H} = 4.6 Hz, 1H).

¹⁹F NMR: δ = -183.72 to -184.00 (m, 1F).

¹³C NMR: δ = 12.03, 13.82, 13.86, 18.64, 21.51, 22.55, 22.80, 23.80, 24.14, 27.99, 28.19, 28.64, 31.47, 34.91, 35.74, 35.99, 36.11, 39.48, 39.81, 41.69, 44.90 (d, *J*_{C,F} = 19.0 Hz), 45.84, 54.68, 56.10, 56.21, 92.33 (d, *J*_{C,F} = 180.3 Hz), 206.90 (d, *J*_{C,F} = 18.2 Hz).

HRMS (EI): *m/z* calcd for C₂₇H₄₅FO: 404.3454; found: 404.3453.

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