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 BF$_3$$\cdot$OEt$_2$ and a Et$_3$N$\cdot$HF complex.

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

Introduction of a fluorine atom into the $\alpha$-position of carbonyl compounds is the most effective method for the synthesis of $\alpha$-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.$^{4}$ Recently we reported that the direct fluorination reaction of $\beta$-dicarbonyl compounds can be achieved using iodotoluene difluoride (ITDF)$^{4,5}$ which can be prepared in large quantity without F$_2$. However, application of ITDF is restricted to $\beta$-dicarbonyl compounds$^{4,5}$ or $\alpha$-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 $\alpha$-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). Zhdankin et al. reported that the iodonium salts can be stably prepared at lower temperature by the reaction of 1 with an iodoarene difluoride-BF$_3$$\cdot$OEt$_2$ complex.$^{13}$ In order to make 2a at low temperature, BF$_3$$\cdot$OEt$_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 °C in the presence of BF$_3$•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 Et$_3$N•HF complexes (Et$_3$N•nHF) could improve the results. When a commercially available Et$_3$N•3HF$^{14,15}$ was used as the fluoride source, 3a could be obtained in 71% yield with a little amount of 4a (9%) and 5a (4%). Et$_3$N•2HF could slightly improve the result but Et$_3$N•HF, TBAF, and Et$_4$NF were less effective than Et$_3$N•2HF or Et$_3$N•3HF.

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-fluorocolesterol were synthesized from their enol esters by the reaction with electrophilic fluorinating regents. 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-fluorocholestan-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
<table>
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<th>Entry</th>
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<th>Product 3</th>
<th>Yield (%)&lt;sup&gt;b&lt;/sup&gt;</th>
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<td>61&lt;sup&gt;c&lt;/sup&gt;</td>
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<sup>a</sup> The reactions were carried out in CH<sub>2</sub>Cl<sub>2</sub> using ITDF, BF<sub>3</sub>•OEt<sub>2</sub>, and Et<sub>3</sub>N•2HF to 1.  <sup>b</sup> Isolated yields based on 1 and yields of olefinic by-products were less than 5 %.  <sup>c</sup> Ratio of cis : trans = 1 : 1
The IR spectra were recorded using a JASCO FT/IR-410. The $^1$H 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, $\delta$, are referred to TMS ($^1$H, $^{13}$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.$^7$ BF$_3$•OEt$_2$ and Et$_3$N•3HF were purchased from Tokyo Kasei Co., Ltd., and distilled under N$_2$ before use. Et$_3$N•2HF and Et$_3$N•HF were prepared by the addition of freshly distilled Et$_3$N to Et$_3$N•3HF. 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$_2$Cl$_2$ solution (10 mL) of ITDF (256 mg, 1.0 mmol) in Teflon FEP vessel$^{21}$ were added at -78 °C, BF$_3$•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 °C for 2 h and a CH$_2$Cl$_2$ solution (5 mL) of Et$_3$N•2HF (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$_2$Cl$_2$ (2×10mL). The combined organic layers were dried over MgSO$_4$ and product 3 was obtained by column chromatography (silica gel/hexane-Et$_2$O).

2-Fluoroacetophenone (3a)

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

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

$^{19}$F NMR $\delta$ = -231.4 (t, $J_{H-F} = 46.8$ 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$^{-1}$.

$^1$H NMR: $\delta$ = 1.64 (d, $J_{H-F} = 38.6$ Hz, 3H), 5.70 (dq, $J_{H-F} = 48.8$, $J_{H-H} = 5.6$ Hz, 1H), 7.48-7.97 (m, 5H).

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

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

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

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

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

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

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

1-Fluoro-2-dodecanone (3e)
IR (neat): 2925, 2855, 1728, 1465, 1047.

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

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

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

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

6-Fluoro-7-tridecanone (3f)

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

$^1$H NMR: $\delta =$ 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, $J_{HF} = 50.4$ Hz, 1H).

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

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

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

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

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

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

$^{19}$F NMR: $\delta =$ -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$^{-1}$.

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

$^{19}$F NMR: $\delta =$ -190.99 (dm, $J_{HF} = 48.2$, 1F) (lit.23 -192 (dm, $J_{HF} = 47.5$ 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$^{-1}$.

$^1$H NMR: $\delta =$ 3.19-3.30 (m, 1H), 3.60-3.68 (m, 1H), 5.27 (dm, $J_{HL} = 51.0$ 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: $\delta =$ -194.17 (ddd, $J_{HF} = 51.0$, 23.2, 7.4 Hz, 1F) (lit.23 -192.5 (ddd, $J_{HF} = 50$, 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$^{-1}$.

$^1$H NMR: $\delta =$ 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, $J_{HL} = 48.5$ Hz, 1H).

$^{19}$F NMR: $\delta =$ -188.62 (dm, $J_{HF} = 48.2$ 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_{HF} = 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_{HF} = 48.1 Hz, 1H).
¹⁹F NMR: δ = -194.67 (dm, J_{HF} = 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_{HF} = 49.8, J_{HH} = 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_{CF} = 19.0 Hz), 45.84, 54.68, 56.10, 56.21, 92.33 (d, J_{CF} = 180.3 Hz), 206.90 (d, J_{CF} = 18.2 Hz).
HRMS (EI): m/z calcd for C_{27}H_{45}FO: 404.3454; found: 404.3453.

References
(19) An equilibrium between two isomers of 7 was not observed under the reaction conditions.
(21) A centrifuge tube with a screw cup made of Teflon FEP, a copolymer of TFE and hexafluoropropylene, was used.