## Instructions for use

### Title
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α-Fluorination of β-dicarbonyl compounds using p-iodotoluene difluoride under neutral conditions

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Dedicated to Professor Anastasios Varvoglis on the occasion of his 65th birthday

Abstract
A selective introduction of a fluorine atom into the α-position of β-dicarbonyl compounds was achieved using p-iodotoluene difluoride. The reaction proceeded under mild conditions and monofluorination of β-ketoesters, ketoamides, and diketones selectively took place.

Keywords: fluorination, p-iodotoluene difluoride, β-dicarbonyl compounds

Introduction
Direct substitution of α-hydrogen of β-dicarbonyl compounds into a fluorine atom is a most efficient method for the synthesis of α-fluoro-β-dicarbonyl compounds which have been used as building blocks for the preparation of biologically active compounds containing a fluorine atom. Elemental fluorine (F₂) or one of the many electrophilic fluorinating agents such as FClO₃, XeF₂, AcOF, R₂OF, and CsSO₄F has been used for the fluorination of β-dicarbonyl compounds. However, most of these agents are highly aggressive, unstable and even explosive, and require special equipment and experience for safe handling. N-Fluorocompounds have been developed as stable and effective fluorinating reagents of carbonyl compounds, but they need F₂ for their preparation and are expensive. We have studied the fluorination of organic compounds using p-iodotoluene difluoride (1) which is not only easy to handle, but also accessible without hazardous F₂ and harmful Hg salts. Recently, we succeeded in the selective fluorination of β-ketoesters (2) using 1 and an HF-amine complex. Though 1 is a stable and safe compound, HF-amine complexes are hazardous. Therefore, we continued to investigate the fluorination reaction of β-carbonyl compounds using 1 to find a more convenient method, and we found the fluorination of β-dicarbonyl compounds using 1 without the addition of the HF-amine complexes (Scheme 1).
Results and Discussion

Table 1. Fluorination of β-ketoesters and β-ketoamides by 1

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Reaction time / h</th>
<th>Yield / %&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[\text{2a}]</td>
<td>10</td>
<td>65</td>
</tr>
<tr>
<td>2</td>
<td>[\text{2b}]</td>
<td>22</td>
<td>72</td>
</tr>
<tr>
<td>3</td>
<td>[\text{2c}]</td>
<td>10</td>
<td>72</td>
</tr>
<tr>
<td>4</td>
<td>[\text{2d}]</td>
<td>12</td>
<td>71</td>
</tr>
<tr>
<td>5</td>
<td>[\text{3a}]</td>
<td>24</td>
<td>74</td>
</tr>
<tr>
<td>6</td>
<td>[\text{3b}]</td>
<td>12</td>
<td>82</td>
</tr>
<tr>
<td>7</td>
<td>[\text{3c}]</td>
<td>24</td>
<td>62</td>
</tr>
</tbody>
</table>

<sup>a</sup> Isolation yields based on substrate used.
The fluorination of β-dicarbonyl compounds under the neutral conditions is slow compared with that under the acidic conditions. When the fluorination of ketoesters 2 using 1 was carried out in the presence of pyridine-9HF, the reaction was completed at room temperature in a few hours.\(^1\) On the other hand, under the neutral conditions, the reaction of pentyl acetoacetate (2a) with 1 was sluggish at room temperature and only a trace of the fluorinated product (5a) was formed after 12 h. When the reaction was carried out at 40 °C in CH\(_2\)Cl\(_2\), 2a was consumed in 10 h and 5a was obtained in 65% yield (Entry 1 in Table 1). Under the similar reaction conditions, various β-ketoesters (2a-d) were selectively monofluorinated, and difluoro products were not formed at all (Entries 1-4 in Table 1). The fluorination of β-ketoamides (3a-c) using 1 was also possible under neutral conditions, and monofluorinated products (6a-c) were obtained in good yield (Entries 5-7).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Reaction time / h</th>
<th>Yield / %(^a)</th>
</tr>
</thead>
</table>
| 1     | \[
\begin{array}{c}
\text{Ph} \\
\text{O} \\
\text{C} \\
\text{C} \\
\text{Ph}
\end{array}
\] 4a | 5       | 71             |
| 2     | 4a       | 2     | 23\(^b\)       |
| 3     | \[
\begin{array}{c}
\text{Ph} \\
\text{O} \\
\text{C} \\
\text{C}
\end{array}
\] 4b | 4     | 62             |
| 4     | 4b       | 2     | 36\(^b\)       |
| 5     | \[
\begin{array}{c}
\text{Ph} \\
\text{O} \\
\text{C} \\
\text{Bu}^t
\end{array}
\] 4c | 2     | 55             |
| 6     | \[
\begin{array}{c}
\text{C}_5\text{H}_{11}
\end{array}
\] 4d | 5     | (71)           |

\(^a\) Isolation yields based on 4 used and in parentheses, NMR yield.
\(^b\) 1 eq. of pyridine-9HF was added.

The fluorination reaction of β-diketones (4) was also examined. In the presence of the amine-HF complex, the reaction of β-diketones (4a,b) with 1 gave the desired monofluoro products (7a,b) in moderate yields with unidentifiable by-products (Entries 2 and 4 in Table 2).
In the reaction of 4a with 1 under the neutral condition, the longer reaction time was required to consume 4a but the monofluoro product 7a could be obtained in good yield (Entry 1). Under the similar conditions, α-unsubstituted β-diketones (4b-d) gave α-fluoro-β-diketones (7b-d) in good yield as shown in Table 2.

**Experimental Section**

**General procedures.** IR spectra were recorded using a JASCO FT/IR-410. 1H and 19F NMR spectra were recorded in CDCl3 on a JEOL JNM-A400 II FT NMR and chemical shifts, δ, are referred to TMS (1H) and CFCl3 (19F) respectively. High-resolution mass spectra were taken at the Center for Instrumental Analysis, Hokkaido University. Silica gel 60N of Kanto Chemical Co., Inc. was used for column chromatography and Merck Silica gel 60 F254 was used for TLC analysis. 1 was prepared from iodotoluene as reported before.10 Ketoesters 2a-c, ketoamide 3a, and diketones 4a-b were purchased from Tokyo Kasei Kogyo Co., Ltd. and used without purification. Pyridine-9HF was prepared from anhydrous HF and pyridine according to the literature.12 Ketoamides 3b-c were prepared from diketene and the corresponding amines according to the literature.13 Ketoester 2d14 and diketones 4c, d15 were prepared according to the literature.

**General procedure for the synthesis of α-fluoro-β-ketoesters (5a-d).**

A CH2Cl2 solution (5 ml) of 2a-d (1 mmol) and 1 (282 mg, 1.1 mmol) in a Teflon® vessel with a screw-cap was stirred at 40 °C. After the reaction, the mixture was poured into 20 ml of aqueous NaHCO3 and extracted with ether (20 ml x 3). The combined organic layers were dried over MgSO4, concentrated under reduced pressure. Purification by column chromatography (silica gel/hexane-ether) gave 5a-d.

**Pentyl 2-fluoro-3-oxobutanoate (5a):** Colorless oil; yield 65%; IR (film) 3462, 2960, 2933, 2873, 2360, 1766(C=O), 1737(C=O), 1468, 1362, 1177, 1107, 966 cm−1; 1H NMR (400 MHz, CDCl3) δ 0.91 (t, J = 6.6 Hz, 3H), 1.31-1.37 (m, 4H), 1.65-1.73 (m, 2H), 2.35 (d, J = 4.1 Hz, 3H), 4.25 (t, J = 6.8 Hz, 2H), 5.20 (d, J = 49.5 Hz, 1H); 19F NMR (376 MHz, CDCl3) δ −193.61 (dq, J = 49.5, 4.1 Hz, 1F); HRMS calcd for C9H15FO3: 190.1005. Found: 190.1003.

**Ethyl 2-fluoro-3-oxohexanoate (5b):** Colorless oil;16 yield 72%; IR (film) 3462, 2960, 2940, 1762(C=O), 1734(C=O), 1467, 1371, 1268, 1222, 1138, 1101, 1021 cm−1; 1H NMR (400 MHz, CDCl3) δ 0.94 (t, J = 6.6 Hz, 3H), 1.33 (t, J = 7.3 Hz, 3H), 1.61-1.70 (m, 2H), 2.58-2.74 (m, 2H), 4.31 (q, J = 7.3 Hz, 2H), 5.20 (d, J = 49.5 Hz, 1H); 19F NMR (376 MHz, CDCl3) δ −195.46 (dt, J = 49.5, 4.1 Hz, 1F); HRMS calcd for C8H13FO3: 190.1005. Found: 190.1003.

**Ethyl 2-fluoro-3-oxo-3-phenylpropionate (5c):** Colorless oil;17 yield 72%; IR (film) 2984, 1762(C=O), 1696(C=O), 1598, 1449, 1246, 1101 cm−1; 1H NMR (400 MHz, CDCl3) δ 1.26 (t, J = 7.1 Hz, 3H), 4.30 (q, J = 7.1 Hz, 2H), 5.87 (d, J = 48.8 Hz, 1H), 7.49-8.06 (m, 5H); 19F NMR (376 MHz, CDCl3) δ −190.90 (d, J = 48.8 Hz, 1F); HRMS calcd for C11H11FO3: 210.0692. Found: 210.0692.
Ethyl 3-cyclohexyl-2-fluoro-3-oxopropionate (5d): Colorless oil; \textsuperscript{17,18} yield 71\%; IR (film) 2934, 2857, 1761(C=O), 1729(C=O), 1450, 1371, 1268, 1209, 1148, 1133, 1098, 1061, 1023 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 1.14-1.58 (m, 5H), 1.32 (t, \(J = 7.2\) Hz, 3H), 1.66-1.92 (m, 5H), 2.83-2.92 (m, 1H), 4.31 (q, \(J = 7.1\) Hz, 2H), 5.27 (d, \(J = 49.3\) Hz, 1H); \textsuperscript{19}F NMR (376 MHz, CDCl\textsubscript{3}) \(\delta\) –196.28 (dd, \(J = 49.3, 3.1\) Hz, 1F); HRMS calcd for C\textsubscript{11}H\textsubscript{17}FO\textsubscript{3}: 216.1162. Found: 216.1141.

General procedure for the synthesis of \(\alpha\)-fluoro-\(\beta\)-ketoamides (6a-c).
A CH\textsubscript{2}Cl\textsubscript{2} solution (5 ml) of 3a-c (1 mmol) and 1 (282 mg, 1.1 mmol) in a Teflon\textsuperscript{®} vessel with a screw-cap was stirred at 40 °C. After the reaction, the mixture was concentrated under reduced pressure and purification by column chromatography (silica gel/hexane-ether) gave 6a-c.

\(N,N\)-Dimethyl-2-fluoro-3-oxobutanamide (6a): Pale yellow oil;\textsuperscript{2e} yield 74\%; IR (film) 3585, 2944, 1740(C=O), 1660(C=O), 1503, 1405, 1360, 1260, 1153, 1079, 830, 611 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 2.35 (d, \(J = 4.1\) Hz, 3H), 3.00 (s, 3H), 3.10 (s, 3H), 5.50 (d, \(J = 50.0\) Hz, 1H); \textsuperscript{19}F NMR (376 MHz, CDCl\textsubscript{3}) \(\delta\) –189.14 (d, \(J = 50.0\) Hz, 1F); HRMS calcd for C\textsubscript{6}H\textsubscript{10}FNO\textsubscript{2}: 147.0695. Found: 147.0706.

\(N,N\)-Diisopropyl-2-fluoro-3-oxobutanamide (6b): Pale yellow oil; yield 82\%; IR (film) 2972, 2938, 1732(C=O), 1650(C=O), 1447, 1373, 1344, 1209, 1138, 1087, 841, 766, 607 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 1.18 (d, \(J = 6.6\) Hz, 3H), 1.22 (d, \(J = 6.6\) Hz, 3H), 1.39 (d, \(J = 6.8\) Hz, 3H), 1.43 (d, \(J = 6.8\) Hz, 3H), 2.32 (d, \(J = 3.9\) Hz, 3H), 3.41-3.52 (m, 1H), 7.62-7.69 (m, 3H), 7.86-7.96 (m, 3H), 8.02-8.09 (m, 3H), 10.01-10.08 (m, 3H); \textsuperscript{19}F NMR (376 MHz, CDCl\textsubscript{3}) \(\delta\) –187.36 (dq, \(J = 50.0, 4.4\) Hz, 1F); HRMS calcd for C\textsubscript{10}H\textsubscript{18}FNO\textsubscript{2}: 203.1321. Found: 203.1329.

1-(2-Fluoro-1,3-dioxobutyl)pyrrolidine (6c): Pale yellow oil; yield 62\%; IR (film) 2977, 2884, 1740(C=O), 1656(C=O), 1446, 1359, 1342, 1217, 1183, 1099, 916, 811 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 1.83-2.05 (m, 4H), 2.36 (d, \(J = 4.4\) Hz, 3H), 3.44-3.59 (m, 3H), 3.65-3.73 (m, 1H), 5.36 (d, \(J = 50.0\) Hz, 1H); \textsuperscript{19}F NMR (376 MHz, CDCl\textsubscript{3}) \(\delta\) –190.76 (dq, \(J = 50.0, 4.4\) Hz, 1F); HRMS calcd for C\textsubscript{8}H\textsubscript{12}FNO\textsubscript{2}: 173.0852. Found: 173.0864.

General procedure for the synthesis of \(\alpha\)-fluoro-\(\beta\)-diketones (7a-d) under the neutral condition.
A CHCl\textsubscript{3} solution (2 ml) of 4a-e (1 mmol) and 1 (333 mg, 1.3 mmol) in a Teflon\textsuperscript{®} vessel with a screw-cap was stirred at room temperature. After the reaction, the mixture was poured into water and extracted with ether (20 ml x 3). The combined organic layers were dried over MgSO\textsubscript{4}, and concentrated under reduced pressure. Purification by column chromatography (silica gel/hexane-ether) gave 7a-e.

General procedure for the synthesis of \(\alpha\)-fluoro-\(\beta\)-diketones (7a,b) in the presence of pyridine-9HF.
To a CH\textsubscript{2}Cl\textsubscript{2} solution (4 ml) of 4a,b (1 mmol) in a Teflon\textsuperscript{®} vessel were added 1 (333 mg, 1.3 mmol) and pyridine-9HF (259 mg, 1 mmol) and the mixture was stirred at room temperature. After the reaction, the mixture was poured into aqueous NaHCO\textsubscript{3} and extracted with ether (20 ml x 3). The combined organic layers were washed with water, aqueous CuSO\textsubscript{4}, and water.
successively, dried over MgSO$_4$, and concentrated under reduced pressure. The purification by column chromatography (silica gel/hexane-ether) gave 7a,b.

2-Fluoro-1,3-diphenyl-1,3-propanedione (7a): White solid; mp 65-66 °C (Lit.$^8$ 66-67 °C); yield 71%; IR (KBr) 2961, 1700 (C=O), 1680 (C=O), 1596, 1449, 1284, 1232 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 6.54 (d, $J$ = 49.1 Hz, 1H), 7.47-7.64 (m, 6H), 8.02-8.11 (m, 4H); $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ -187.47 (d, $J$ = 49.1 Hz, 1F); HRMS calcd for C$_{15}$H$_{11}$FO$_2$: 242.0743. Found: 242.0746. Anal. Calcd for C$_{15}$H$_{11}$FO$_2$: C, 74.37; H, 4.58; F, 7.84. Found: C, 74.46; H, 4.67; F, 7.54.

2-Fluoro-1-phenyl-1,3-butanedione (7b): Clear liquid; yield 62%; IR (film) 2923, 1737 (C=O), 1695 (C=O), 1599, 1480, 1449, 1359, 1277 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 2.34-2.36 (m, 3H), 5.95 (d, $J$ = 48.8 Hz, 0.6 H), 7.45-7.66 (m, 3H), 7.94-8.03 (m, 2H), 13.72 (d, $J$ = 3.5 Hz, 0.4H); $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$: -190.16 (dq, $J$ = 48.8, 3.8 Hz, 0.6F), -170.71- -170.67 (m, 0.4F); HRMS calcd for C$_{10}$H$_9$FO$_2$: 180.0586. Found: 180.0632.

2-Fluoro-1-phenyl-4,4-dimethyl-1,3-pentanedione (7c): Clear liquid; yield 55%; IR (film) 2974, 1719 (C=O), 1693 (C=O), 1599, 1480, 1367, 1210 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 1.25 (s, 5.4H), 1.32 (s, 3.6H), 6.15 (d, $J$ = 49.3 Hz, 0.6H), 7.45-8.11 (m, 5H), 14.25 (d, $J$ = 3.7 Hz, 0.4H). $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$: -187.75 (d, $J$ = 49.3 Hz, 0.6F), -167.99 (s, 0.4F); HRMS calcd for C$_{13}$H$_{15}$FO$_2$: 222.1056. Found: 222.1049.

3-Fluoro-2,4-nonanedione (7d): Clear liquid; yield 71% yield was determined by $^1$H NMR using methyl benzoate as internal standard; IR (film) 2958, 2933, 1743 (C=O), 1721 (C=O), 1600, 1466, 1360 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 0.89 (t, $J$ = 6.8 Hz, 3H), 1.26-1.33 (m, 4H), 1.56-1.68 (m, 2H), 2.30 (d, $J$ = 3.9 Hz, 3H), 2.47-2.73 (m, 2H), 5.24 (d, $J$ = 50.5 Hz, 1H); $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$: -193.68 (dm, $J$ = 50.5 Hz, 1F); HRMS calcd for C$_9$H$_{15}$FO$_2$: 174.1056. Found: 174.1060.

References