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# Simple procedure for preparation of α-fluoro esters by fluorination of ester enol silyl ethers with perchloryl fluoride

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Dedicated to Professor Lev M. Yagupolskii on the occasion of his 80th birthday.

## Abstract

Fluorination of ester enol silyl ethers in THF at room temperature using diluted perchloryl fluoride ($FClO_3$) in the presence of ca. 0.5 M eq. of $t$-$BuNH_2$ as an additive produced the corresponding α-fluoro esters in over 80% yields.

*Keywords:* α-Fluoro ester; Perchloryl fluoride; Ester enol silyl ether

## 1. Introduction

In the course of preparing a key intermediate for the synthesis of fluorine-containing potential medicinals, we encountered the need for a practical synthesis of α-fluoro esters. In contrast to the case of enolizable ketones, direct fluorination of esters has been problematic. Two groups reported direct fluorination of α-substituted esters with perchloryl fluoride ($FClO_3$) to afford α-substituted α-fluoro esters [1]. However, there has been no successful report describing the fluorination of α-unsubstituted esters. An alternative route to α-fluoro esters involves fluorination of enol silyl ethers, derived from esters, with $CF_3OF$ [2], *N*-fluoropyridinium triflate (FP-T500®) [3], or 5% $F_2/N_2$ [4]. However, all of these fluorinations require the use of sensitive reagents and/or lack generality.

We report here a practical method for the general preparation of α-fluoro esters by fluorination of the corresponding enol silyl ethers using diluted $FClO_3$ in the presence of a half molar equivalent of amine compound.

## 2. Results and discussion

We first attempted direct fluorination of esters with $FClO_3$, following a procedure similar to the literature method [1]. Since this hazardous reagent is no longer commercially available, we employed a reliable and safe procedure, which involves the slow generation of $FClO_3$ [5] and entrainment as a diluted gas in $N_2$ [6]. A solution of the lithium enolate of ester **1a** in THF, formed by treatment with LDA by the usual procedure, was subjected to slow introduction of diluted $FClO_3$ at −50 °C for 60 min. This produced the α-fluoro ester **2a** in 56% yield. However, attempted application of this procedure to the esters **1b** and **1c** gave the corresponding α-fluoro esters **2b** and **2c** only in trace yields. Attempted fluorination of **1a** with FP-T500® [3] to produce **2a** was unsuccessful (Scheme 1). These results can be ascribed to the difficulty in generating the stable carbanion at the position α to the ester groups.

As a strategy to avoid this complication of lithium enolate instability, we focused on fluorination of the corresponding enol silyl ethers. Ester enol silyl ethers were prepared by treatment of the esters with LDA and TMSCl, according to the reported general procedure [7]. We first attempted fluorination of silyl ether **3a** with 15% $F_2$/He under various conditions [4]. Since the enol silyl ether was sensitive to acid and slowly decomposed during reaction, some bases were used as additives. However, the results were unsatisfactory (Scheme 2).

We next attempted fluorination of **3a** with diluted $FClO_3$ generated by our procedure [6]. Temperature, additive, and solvent were examined in order to optimize the reaction conditions. We found that the presence of a base is important to this reaction and the use of ca. 0.5 M eq. of amine as an additive seemed to be generally effective (Table 1).

We then investigated the kinds of amine compounds most suitable for this fluorination. The best result was obtained

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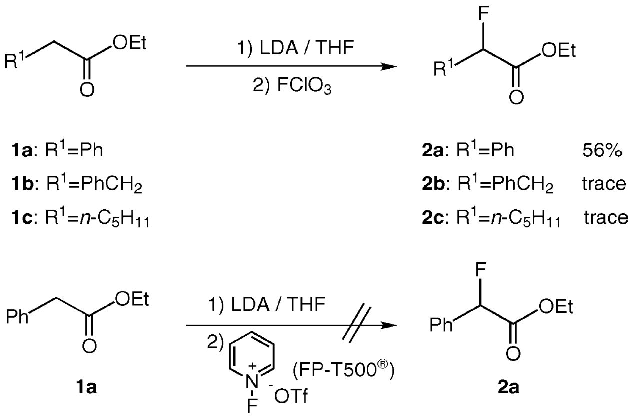
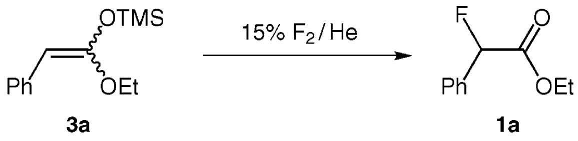


Scheme 1. Fluorination of esters **1**.

when enol silyl ether **3a** in THF was subjected to our $FClO_3$ fluorination for 30 min at room temperature, with 0.5 M eq. of $t$-$BuNH_2$ as an additive, to give **2a** in 83% yield. In the case of fluorination of **3a** with FP-T500®, an amine compound seemed not to be important (Table 2).

In order to see the generality of this reaction, several ester enol silyl ethers **3b–f** were subjected to our fluorination using 0.5 M eq. of $t$-$BuNH_2$ as an additive. The corresponding α-fluoro esters **2b–f** were obtained in excellent yields (Table 3).

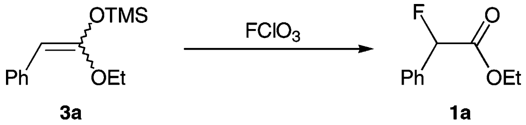


| additive (eq.) | solvent | time (min) | yield (%) |
|---|---|---|---|
| — | $CHCl_3$ | 5 | 9 |
| — | $CFCl_3$ | 5 | 37 |
| NaF (3.0) | $CFCl_3$ | 5 | 37 |
| KF (3.0) | $CFCl_3$ | 5 | 40 |
| $Et_3N$ (1.0) | $CFCl_3$ | 5 | trace |
| $K_2CO_3$ (3.0) | $CFCl_3$ | 5 | 25 |

Scheme 2. Reaction of enol silyl ether **3a** with 15% $F_2$ in He.

Enol ethers derived from ketones are usually fluorinated with $FClO_3$ in basic conditions, such as in pyridine solvent, to produce α-fluoroketones [8]. In contrast, enol silyl ethers derived from esters are rather unstable under basic conditions, especially in the presence of moisture, and they, therefore,

Table 1
Reaction of enol silyl ether **3a** with $FClO_3$

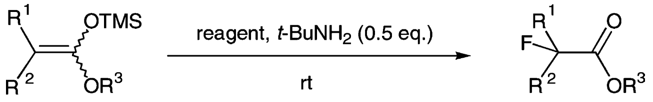


| Additive (eq.) | Solvent | Temperature | Time (min) | Yield (%) |
|---|---|---|---|---|
| – | $CHCl_3$ | RT | 15 | Trace |
| – | THF | RT | 15 | 45 |
| $Et_3N$ (0.1) | THF | RT | 15 | 22 |
| $Et_3N$ (0.5) | THF | RT | 15 | 53 |
| $Et_3N$ (1.0) | THF | RT | 15 | 44 |
| $Na_2CO_3$ (1.0) | THF | RT | 15 | 38 |
| Pyridine (1.0) | THF | RT | 15 | 38 |
| $Et_3N$ (0.5) | THF | RT | 30 | 67 |
| $Et_3N$ (0.5) | THF | 0 °C | 30 | 56 |
| $Et_3N$ (0.5) | THF | −78 °C | 30 | 73 |

Table 2
Reaction of **3a** with $FClO_3$ using 0.5 M eq. of amine compounds

| Reagent | Additive (eq.) | Solvent | Temperature | Time (min) | Yield (%) |
|---|---|---|---|---|---|
| $FClO_3$ | ($i$-$Pr)_2NH$ (0.5) | THF | RT | 30 | 63 |
| $FClO_3$ | ($p$-$H_2N$-Ph–$)_2$ | THF | RT | 30 | 21 |
| $FClO_3$ | PhNHMe (0.5) | THF | RT | 30 | 45 |
| $FClO_3$ | $PhCHMeNH_2$ (0.5) | THF | RT | 30 | 80 |
| $FClO_3$ | $PhCHMeNH_2$ (0.5) | THF | −78 °C | 30 | 71 |
| $FClO_3$ | $t$-$BuNH_2$ (0.5) | THF | RT | 30 | 83 |
| FP-T500® | – | $CH_2Cl_2$ | RT | 120 | 59 |
| FP-T500® | $t$-$BuNH_2$ (0.5) | $CH_2Cl_2$ | RT | 120 | 50 |

Table 3
Fluorination of enol silyl ethers **3b–f**



| Silyl ether | $R^1$ | $R^2$ | $R^3$ | Reagent | Solvent | Time (min) | Product | Yield (%) |
|---|---|---|---|---|---|---|---|---|
| **3b** | $PhCH_2$ | H | Et | $FClO_3$<br>FP-T500® | THF<br>$CH_2Cl_2$ | 30<br>120 | **2b** | 83<br>13 |
| **3c** | $n$-$C_5H_{11}$ | H | Et | $FClO_3$<br>FP-T500® | THF<br>$CH_2Cl_2$ | 30<br>120 | **2c** | 88<br>13 |
| **3d** | Et | H | $CH_2Ph$ | $FClO_3$ | THF | 30 | **2d** | 92 |
| **3e** | Me | H | Bu | $FClO_3$ | THF | 30 | **2e** | 100 |
| **3f** | $-(CH_2)_5-$ | | Me | $FClO_3$ | THF | 20 | **2f** | 92 |

slowly decompose into the original esters in the presence of excess of amine compound. However, reaction with $FClO_3$ in the presence of even small amount of moisture seems to make the medium acidic and this also leads to decomposition of the silyl ethers. Because of this, we feel an important factor necessary to carry out this delicate fluorination effectively is the careful control of the nature of the medium to avoid decomposition of the rather unstable ester enol ethers during reaction. However, additional study may be necessary to clear the role of amine compound in this fluorination.

## 3. Conclusion

In contrast to α-chlorination or α-bromination of esters, practical procedures for α-fluorination of esters have been problematic. With this in mind, we have developed a simple procedure for this purpose using $FClO_3$ fluorination of ester enol silyl ethers in the presence of suitable amount of a base.

## 4. Experimental

IR spectra were obtained on a Perkin-Elmer 1600 (ET-IR) spectrophotometer. $^1H$ and $^{19}F$ NMR spectra were obtained with a JEOL GX-270 (270.05 MHz for $^1H$ and 254.19 MHz for $^{19}F$) spectrometer in $CDCl_3$ with $Me_4Si$ or $CFCl_3$ as an internal reference. Mass spectra were measured on a JEOL JMS-GCmate. High-resolution mass spectra were obtained using a JEOL JMS-AX 505 HAD. Commercially available FP-T500® was used [3]. Enol silyl ethers were prepared according to the reported procedure [7]. Silica gel (Fuji Silysia BW-200) was used for column chromatography.

### *4.1. General procedure for preparation of α-fluoro esters by $FClO_3$ fluorination of the corresponding ester enol silyl ethers*

A mixture of potassium perchlorate (0.5 g, 3.6 mmol) in fluorosulfonic acid (2 ml, 34.8 mmol) was charged into a 20 ml two-necked flask equipped with stirrer and reflux condenser and was heated in an oil bath. The bath temperature was raised gradually and was finally kept around 90 °C. After about 10 min, $FClO_3$ started to be evolved [5]. The freshly generated $FClO_3$ was entrained as a diluted gas in nitrogen [6] and introduced into a solution of aqueous 10% sodium hydroxide containing 5% sodium thiosulfate. The scrubbed gases were passed over solid sodium fluoride and then solid calcium chloride [5].

The diluted $FClO_3$ gas thus prepared was introduced into a solution of ester enol silyl ether **3** (0.2 mmol) and $t$-$BuNH_2$ (0.1 mmol) in dry THF (0.5 ml) at room temperature for 20–30 min. The resulting mixture was concentrated to give an oil, dissolved in $CHCl_3$ and filtered through silica gel to remove polar substances. Removal of solvent gave α-fluoro ester **2** contaminated with a small amount of starting material **1**. Yields were calculated based on $^1H$ NMR.

### *4.2. Ethyl 2-fluoro-2-phenylacetate (**2a**) [2]*

Yield: 83%; colorless oil; IR (neat) 1735 (C=O) cm$^{-1}$; $^1H$ NMR $\delta$ (ppm) 1.26 (t, $J = 7.3$ Hz, 3H), 4.25 (m, 2H), 5.77 (d, $J = 47.8$ Hz, 1H), 7.39–7.46 (m, 5H); $^{19}F$ NMR $\delta$ (ppm) −180.37 (d, $J = 47.3$ Hz, 1F); MS $m/z$ 182 ($M^+$), 163 ($M^+ - F$), 109 ($M^+ - COOEt$), 90 ($M^+ - COOEt - F$); HRMS $m/z$ calcd. for $C_{10}H_{11}FO_2$ ($M^+$): 182.0743, found: 182.0744.

### *4.3. Ethyl 2-fluoro-3-phenylpropanoate (**2b**) [9]*

Yield: 83%; colorless oil; IR (neat) 1734 (C=O) cm$^{-1}$; $^1H$ NMR $\delta$ (ppm) 1.11 (t, $J = 7.2$ Hz, 3H), 2.93–3.19 (m, 2H), 4.08 (q, $J = 7.2$ Hz, 2H), 4.95 (ddd, $J = 48.9$, 7.4, 4.5 Hz, 1H), 7.06–7.21 (m, 5H); $^{19}F$ NMR $\delta$ (ppm) −190.30 (dt, $J = 49.2$, 24.2 Hz, 1F); MS $m/z$ 196 ($M^+$), 177 ($M^+ - F$), 122 ($M^+ - COOEt$), 103 ($M^+ - COOEt - F$); HRMS $m/z$ calcd. for $C_{11}H_{13}FO_2$ ($M^+$): 196.0900, found: 196.0909.

### 4.4. *Ethyl 2-fluoroheptanoate (**2c**)*

Yield: 88%; colorless oil; IR (neat) 1739 (C=O) $cm^{-1}$; $^1H$ NMR $\delta$ (ppm) 1.27–1.52 (m, 12H), 1.79–1.96 (m, 2H), 4.26 (q, $J = 7.1$ Hz, 2H), 4.89 (ddd, $J = 48.9, 5.9, 5.9$ Hz, 1H); $^{19}F$ NMR $\delta$ (ppm) −192.48 (dt, $J = 49.9, 25.0$ Hz, 1F); MS *m/z* 176 ($M^+$), 103 ($M^+ -$ COOEt), 84 ($M^+ -$ COOEt − F); HRMS *m/z* calcd. for $C_9H_{17}FO_2$ ($M^+$): 176.1213, found: 176.1211.

### 4.5. *Phenylmethyl 2-fluorobutanoate (**2d**)*

Yield: 92%; colorless oil; IR (neat) 1737 (C=O) $cm^{-1}$; $^1H$ NMR $\delta$ (ppm) 0.98 (t, $J = 7.4$ Hz, 3H), 1.67–1.99 (m, 2H), 4.87 (ddd, $J = 49.0, 6.8, 6.8$ Hz, 1H), 5.20 (s, 2H), 7.34 (brs, 5H); $^{19}F$ NMR $\delta$ (ppm) −193.99 (dt, $J = 48.8, 24.8$ Hz, 1F); MS *m/z* 196 ($M^+$), 177 ($M^+ -$ F); HRMS *m/z* calcd. for $C_{11}H_{13}FO_2$ ($M^+$): 196.0900, found: 196.0897.

### 4.6. *Butyl 2-fluoropropanoate (**2e**)*

Yield: 100%; colorless oil; IR (neat) 1740 (C=O) $cm^{-1}$; $^1H$ NMR $\delta$ (ppm) 0.87 (t, $J = 7.3$ Hz, 3H), 1.26–1.69 (m, 7H), 4.13 (t, $J = 6.3$ Hz, 2H), 4.93 (dq, $J = 48.5, 6.9$ Hz, 1H); $^{19}F$ NMR $\delta$ (ppm) −184.86 (dq, $J = 48.0, 24.0$ Hz, 1F); MS *m/z* 148 ($M^+$), 129 ($M^+ -$ F); HRMS *m/z* calcd. for $C_7H_{13}FO_2$ ($M^+$): 148.0900, found: 148.0898.

### 4.7. *Methyl 1-fluorocyclohexanecarboxylate (**2f**) [10]*

Yield: 92%; colorless oil; IR (neat) 1739 (C=O) $cm^{-1}$; $^1H$ NMR $\delta$ (ppm) 1.64–1.96 (m, 10H), 3.78 (s, 3H); $^{19}F$ NMR $\delta$ (ppm) −165.50 (brs, 1F); MS *m/z* 160 ($M^+$), 141 ($M^+ -$ F), 101 ($M^+ -$ COOMe), 82 ($M^+ -$ COOMe − F); HRMS *m/z* calcd. for $C_8H_{13}FO_2$ ($M^+$): 160.0900, found: 160.0901.

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