Selective fluorination of β-ketoesters using iodotoluene difluoride and a HF–amine complex

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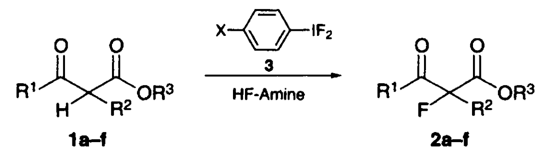
β-Ketoesters are selectively fluorinated at the α-position by iodotoluene difluoride and a HF–pyridine complex.

This is the first paper in a series investigating the synthetic utility of iodotoluene difluoride. Although the iodotoluene difluoride in this paper was prepared *via* Carpenter's original HgO method, a recent paper[1] describes a potentially more practical, regenerative method.

2-Fluoro-1,3-dicarbonyl compounds have been synthesized by treating the parent dicarbonyls or their enolates with elemental fluorine[2] or one of the many electrophilic fluorinating agents such as $FClO_3$,[3] XeF_2,[4] AcOF,[5] R_FOF[6] and $CsSO_4F$.[7] However, most of these agents are highly reactive, unstable and even explosive, and require special equipment and experience for safe handling. Recently, *N*-fluoro compounds[8] have been developed as stable and effective fluorinating reagents of carbonyl compounds, but elemental fluorine is necessary for their preparation. On the other hand, iodoarene difluorides **3** are an attractive fluorinating reagent as they are synthetically accessible without the use of fluorine.[9] Although iodoarene difluorides **3** have been successfully used for the fluorination of alkenes[10] and sulfur compounds,[11] they have not been applied for the direct fluorination of carbonyl compounds. We report here that the β-ketoesters **1** reacted with iodoarene difluorides **3** in the presence of a HF–amine complex to give α-fluorinated products **2** (Scheme 1).

The fluorination of butyl acetoacetate **1b** was carried out using iodoarene difluorides **3** and a variety of amine–HF complexes as shown in Table 1. Iodobenzene difluoride **3a** alone showed no reactivity towards **1b**, but in the presence of an amine–HF complex such as *n*HF–pyridine and *n*HF–Et_3N, the fluorination of **1b** took place selectively at the α-position to give the corresponding fluorinated products **2b**.†,‡ Among the amine–HF complexes used, the 9HF–pyridine complex (Olah's reagent) gave the best results. As for the iodoarene difluorides **3**, *p*-iodotoluene difluoride **3b** was found to be superior to **3a** and the ethyl *p*-iodobenzoate derivative **3c**. The reaction of the β-ketoesters **1a–d** having no substituent at the α-position with 1 equiv. of the 9HF–pyridine complex and 1.3 equiv. of **3b** in dichloromethane proceeded at room temperature to give the α-fluoro compounds **1a–d** in good yields. The formation of difluoro products was not observed (less than 1% yield) under these reaction conditions. The reaction of α-substituted ketoesters **1e–f** was less satisfactory and the yields of the fluorinated products **2e–f** are lower than those of the unsubstituted ones **2a–d**, Table 2.



Scheme 1

Table 1 Fluorination of butyl acetoacetate with iodoarene difluorides and HF–amine complexes

Iodoarene difluoride 3	X	HF–Amine	Reaction time/h	Yield of 2b (%)[a]
a	H	none	72	0
a	H	3HF–Et_3N	41	60
a	H	6HF–Et_3N	8	57
a	H	3HF–pyridine	25	25
a	H	6HF–pyridine	5	62
a	H	9HF–pyridine	3	62
b	Me	9HF–pyridine	3	79
c	COOEt	9HF–pyridine	3	30

[a] Isolated yield based on butyl acetoacetate

Table 2 Fluorination of β-ketoesters with **3b**

β-ketoester 1	R^1	R^2	R^3	Reaction time/h	Yield of 2 (%)[a]
a	Me	H	Et	2	(80)
b	Me	H	Bu	3	79
c	Pr	H	Et	3	72
d	Ph	H	Et	3	73
e	Me	Me	Bu	3	62
f	Ph	Ph	Et	5	(50)

[a] Isolated yields based on **1**. GLPC Yields in parentheses.

Footnotes

† *Typical experimental procedure*: To a solution of **1b** (316 mg, 2 mmol) in CH_2Cl_2 (10 ml) in a reaction vessel made from Teflon PFA™ was added 9HF–pyridine (518 mg, 2 mmol) and **3b** (663 mg, 2.6 mmol). The mixture was stirred at room temp. for 3 h and aqueous sodium hydrogen carbonate was added to neutralize the mixture. The mixture was then extracted with diethyl ether (3×) and the combined organic layers were washed with aqueous copper sulfate to remove pyridine and then with water. The organic layer was dried ($MgSO_4$) and concentrated under vacuum. Purification by column chromatography (silica gel, dichloromethane) gave **2b** in 79% yield.

‡ *Spectra data* for **2b**: ^1H NMR (400 MHz, $CDCl_3$) δ 0.942 (t, *J* 7.3 Hz, 3 H), 1.34–1.73 (m, 4 H), 2.3496 (d, *J* 4.1 Hz, 3 H), 4.26 (t, *J* 6.6 Hz, 2 H), 5.20 (d, *J* 52.0 Hz, 1 H); ^{19}F NMR (375 MHz, $CDCl_3$)($CFCl_3$ as an internal standard) δ −193.56 (d, *J* 52.5 Hz); IR (neat) ν/cm^{-1} 1750 and 1730 (HRMS: Calc. for $C_8H_{13}O_3F$: 176.0849. Found, 176.0844).

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