## Nickel Catalyzed Reaction of Iodofluoroacetates with Alkenes as a Facile Route to $\alpha$ -Fluoroesters

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Abstract: Reaction of iodofluoroacetates with alkenes and zinc in the presence of nickel dichloride hexahydrate and pyridine in THF affords the corresponding  $\alpha$ -fluoroesters in good yields.

The introduction of fluorine into an organic molecule leads to changes in biological activity.<sup>1,2</sup> In recent years,  $\alpha$ -fluoroalkanoates have attracted much attention in biochemistry since they have been utilized as analytical probes and diagnostic tools in metabolic processes.<sup>3</sup> In addition,  $\alpha$ -fluoroalkanoates have served as useful building blocks to synthesize more complex and biologically interesting molecules.<sup>4</sup> Although several methods for the preparation of  $\alpha$ -fluoroalkanoates, such as alkylation of fluoroacetate ions,<sup>5</sup> fluorination of enolates,<sup>6</sup> and fluorination of silyl enol ethers,<sup>7</sup> have been documented in the literature, limitations with these methods restrict their utility in organic synthesis.

More recently, work in our group has demonstrated the utility of  $\alpha$ -fluorocarboalkoxy phosphorus ylides prepared from bromofluoroacetates as a facile entry to  $\alpha$ -fluoroesters.<sup>8</sup> Although reaction with primary and activated halides provides reasonable yields of  $\alpha$ -fluoroesters, none of the desired products are formed with secondary halides, and some functionalities can not be tolerated under the reaction conditions. In the continous effort to explore new methodologies for the preparation of  $\alpha, \alpha$ -difluoro functionalized compounds catalyzed by metals or organometallic complexes,<sup>9</sup> recently we discovered that the nickel catalyzed reaction of iododifluoroacetates with alkenes gave the corresponding  $\alpha, \alpha$ -difluoroesters. Now we wish to describe a nickel catalyzed reaction of iodofluoroacetates with unsaturated substrates as a new and direct method for the preparation of  $\alpha$ -fluoroesters.

Initially, when ethyl iodofluoroacetate 1 was treated with 1.5 equivalents of 1-hexene and zinc in the presence of 5 mol% NiCl<sub>2</sub>·6H<sub>2</sub>O in THF at 60 °C, ethyl  $\alpha$ -

fluorooctanoate and fluoroacetate were formed in a 1:1 ratio. On addition of pyridine (2 equiv. relative to NiCl<sub>2</sub>.6H<sub>2</sub>O), the ratio of  $\alpha$ -fluorooctanoate to fluoroacetate increased to 3:1. Finally, we found that when four equivalents of alkene were employed, reaction of iodofluoroacetates 1<sup>10</sup> proceeds readily with zinc in the presence of NiCl<sub>2</sub>.6H<sub>2</sub>O and pyridine to afford the corresponding  $\alpha$ -fluoroacetates in good yields, and only small amounts (5%) of the toxic fluoroacetate

$$\begin{array}{rcl} \text{ICHFCO}_2 \text{R} & + & \text{CH}_2 = \text{CHR'} & \frac{\text{NiCl}_2 \cdot 6\text{H}_2 \text{O}}{\text{Zn/Py/THF}} & \text{R'CH}_2 \text{CH}_2 \text{CHFCO}_2 \text{R} \\ 1 & & 60 \ ^{\circ}\text{C} \end{array}$$

were detected by <sup>19</sup>F NMR analysis of the reaction mixture. The reaction is also applicable to alkenes containing functionalities such as trimethylsilyl and ketone. When diallylether was used as a substrate, a tetrahydrofuran derivative was obtained. However, when ethyl 2-methyl-4-pentenoate was used as a substrate, the  $\alpha$ -monofluoroester was formed only in 50% yield with 50% of fluoroacetate even if a large excess 1 was employed. With electron deficient alkenes or internal alkenes such as ethyl acrylate and cyclohexene under the similar conditions, none of the desired products were formed and only fluoroacetate was observed. The results of this exploratory study are summarized in Table I.

In a typical experiment, a three-necked flask equipped with a stir bar, a rubber septum, and a condenser topped with a nitrogen inlet was charged with 0.4 g (1.7 mmol) of NiCl<sub>2</sub>·6H<sub>2</sub>O, 2.6 g (40 mmol) of zinc and 20 mL of THF. After the mixture was stirred at room temperature for 10 minutes, 0.26 g (3.3 mmol) of pyridine was added and the mixture was stirred for 20 minutes, then 6.7 g (80 mmol) of 1-hexene and 4.6 g (20 mmol) of ethyl iodofluoroacetate were added at 60°C and the resultant mixture was stirred for 3.5 hours. The reaction mixture was poured into saturated NH<sub>4</sub>Cl solution and extracted with 400 mL of a mixture of pentane and ether (1:1). The combined organic layers were washed with water and dried over anhydrous MgSO4. After evaporation of the solvents, the residue was distilled at reduced pressure to give 2.8 g (73%) of ethyl 2-fluorooctanoate, 99% GLPC purity, b.p. 79-81°C/0.5 mmHg. <sup>1</sup>H NMR(CDCl<sub>3</sub>, TMS): 4.89 (dt, <sup>2</sup>J<sub>F,H</sub> = 49 Hz,  ${}^{3}J_{H,H} = 6$  Hz, 1H), 4.26 (q,  ${}^{3}J_{H,H} = 7$  Hz, 2H), 1.89 (m, 2H), 1.38(m, 10H), 0.89(t,  ${}^{3}J_{H,H} = 6$ 7 Hz, 3H); <sup>19</sup>F NMR (CDCl<sub>3</sub>, CFCl<sub>3</sub>): -192.5 (dt,  ${}^{2}J_{F,H} = 50$  Hz,  ${}^{3}J_{F,H} = 25$  Hz); <sup>13</sup>C NMR(CDCl<sub>3</sub>, TMS): 170.2(d,  ${}^{2}J_{F,C} = 24$  Hz), 89.1(d,  ${}^{1}J_{F,C} = 184$  Hz), 61.4, 32.5 (d,  ${}^{2}J_{F,C} = 184$  Hz), 61.4 21 Hz), 31.6, 28.8, 24.4, 22.6, 14.2, 14.0; FT-IR(CCl<sub>4</sub>): 2959 (s), 2931(s), 1766(s), 1741(s), 1280(s), 1190(s), 1091(s); GC-MS:  $161(M^+-C_2H_5, 6.7)$ , 129(10.5), 106(100), 101(11.8), 78(47.3), 69(10.5), 55(65.0), 43(51.9).

ICHFCO₂R	+ СН₂=СН	R' NiCl <sub>2</sub> -6H <sub>2</sub> O Zn/Py/THF 60 °C	IFCO₂R	
R'	R	Product	Yield <sup>a</sup>	Purity <sup>b</sup>
n-C4H9	C <sub>2</sub> H <sub>5</sub>	n-C6H13CFHCO2C2H5	73	99
n-C <sub>6</sub> H <sub>13</sub>	C <sub>2</sub> H <sub>5</sub>	n-C8H17CFHCO2C2H5	70	98
CH <sub>3</sub> CO(CH <sub>2</sub> ) <sub>2</sub>	C <sub>2</sub> H <sub>5</sub>	CH <sub>3</sub> CO(CH <sub>2</sub> ) <sub>4</sub> CFHCO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	62	97
n-C <sub>2</sub> H <sub>5</sub>	CH(CH <sub>3</sub> ) <sub>2</sub>	n-C4H9CFHCO2CH(CH3)2c	61	96
EtO2CCHMeCH2	C <sub>2</sub> H <sub>5</sub>	EtO2CCHMe(CH2)3CFHCO2Et	50d	
n-C4H9	CH(CH <sub>3</sub> ) <sub>2</sub>	n-C6H13CFHCO2CH(CH3)2	80	96
n-C <sub>6</sub> H <sub>13</sub>	CH(CH <sub>3</sub> ) <sub>2</sub>	n-C8H17CFHCO2CH(CH3)2	75	98
Me <sub>3</sub> Si	CH(CH <sub>3</sub> ) <sub>3</sub>	Me3SiCH2CH2CFHCO2CH(CH3)2	77	98
CH2=CHCH2OCH2	$C_2H_5$	CF <sub>2</sub> CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	57 <sup>e</sup>	97

Table I Preparation of  $\alpha$ -Fluoroalkanoates Catalyzed by Nickel

a) Isolated yields. All products gave satisfactory <sup>19</sup>F, <sup>1</sup>H, <sup>13</sup>C NMR, FT-IR and GC/MS data.

- b) Determined by GLPC.
- c) Reaction was carried out in a sealed tube.
- d) Yield was determined by <sup>19</sup>F NMR; 50% of CFH<sub>2</sub>CO<sub>2</sub>Et was also observed.

e) trans/cis = 3:1.

In conclusion, we have demonstrated the nickel catalyzed addition reaction of iodofluoroacetates with terminal alkenes. This methodology for the preparation of  $\alpha$ -fluoroesters avoids the utilization of toxic and hazardous materials and extreme reaction conditions. The ready availability of suitable catalysts and precursors and the simplicity of the experimental procedure makes this approach a convenient method for the preparation of biologically important  $\alpha$ -fluoroesters.

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