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## Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information: http://www.tandfonline.com/loi/lsyc20

# Practically useful Reformatsky Type Reactions of Chlorodifluoroacetate and Bromodifluoroacetate Induced by Samarium(II) Diiodide

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To cite this article: Masato Yoshida , Daiki Suzuki & Masahiko Iyoda (1996) Practically useful Reformatsky Type Reactions of Chlorodifluoroacetate and Bromodifluoroacetate Induced by Samarium(II) Diiodide, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 26:13, 2523-2529, DOI: 10.1080/00397919608004565

To link to this article: http://dx.doi.org/10.1080/00397919608004565

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## PRACTICALLY USEFUL REFORMATSKY TYPE REACTIONS OF CHLORODIFLUOROACETATE AND BROMODIFLUOROACETATE INDUCED BY SAMARIUM(II) DIIODIDE

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<u>Abstract</u>: Treatment of XCF<sub>2</sub>COOEt (X = Cl and Br) with SmI<sub>2</sub> in THF gave efficiently  $\beta$ ,  $\beta$ -difluorinated enolate equivalent, which was used for Reformatsky type reaction with aldehydes and ketones to give 2,2-difluoro-3-hydroxy ester.

Recently,  $\alpha, \alpha$ -difluorinated compounds have been attracted much attentions due to their unique physical, chemical and biological properties.<sup>1</sup> Reformatsky reaction is known to be one of the most useful methods for the construction of  $\alpha, \alpha$ -difluorinated compounds from XCF<sub>2</sub>COOR (X = I, Br, and Cl) using Zn to induce the reaction.<sup>2</sup> After the initial report of Hallinan and Fried,<sup>3</sup> several modified methods have been investigated mainly from the view of the activation of

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Zn to realize the reaction efficiently by the use of additives<sup>4</sup> or sonicating conditions.<sup>5</sup> Now, we found that samarium(II) diiodide  $(SmI_2)^6$  as an alternative reagent to Zn realized the reactions of XCF<sub>2</sub>COOEt (X = Cl and Br) with aldehydes and ketones giving 2, 2-difluoro-3-hydroxy esters effectively and practically at room temperature, and the results are described in this communication.

$$XCF_{2}COOEt \xrightarrow{1) 2 Sml_{2}, RCOR' 2) aq-HCl}_{HO} \xrightarrow{R'}_{R}$$

When a solution of XCF<sub>2</sub>COOEt (X=Cl and Br) and aldehyde or ketone in THF was added to a solution of SmI<sub>2</sub> in THF at room temperature under nitrogen, the color of the solution turned from purple to yellow at once, indicating the end of the reaction. Sufficient yields were obtained in both aldehydes and ketones other than bezaldehyde as shown in Table. Benzaldehyde itself reacted with SmI<sub>2</sub> and prevented the effective reaction of BrCF<sub>2</sub>COOEt with SmI<sub>2</sub>. In two step procedure, only trace amount of desired product was obtained; BrCF<sub>2</sub>COOEt was added to the solution of SmI<sub>2</sub> in THF under nitrogen, during which the characteristic color of SmI<sub>2</sub> disappeared, and then 2-octanone was added to the resulting solution in stepwise. Though the nature of the reactive intermediate produced by the reaction of BrCF<sub>2</sub>COOEt with SmI<sub>2</sub> is not yet clear,  $\beta$ ,  $\beta$ difluorinated enolate equivalent to react with 2-octanone should form at first but immediately turned to quite stable species, which no longer reacted with the ketone.

The SmI<sub>2</sub>-induced reactions were completed within 1 min at room temperature in both BrCF<sub>2</sub>COOEt and ClCF<sub>2</sub>COOEt. Meanwhile, Zn-induced reactions of ClCF<sub>2</sub>COOEt failed under the reaction conditions which are normally

RCOR'	XCF <sub>2</sub> COOEt	Method <sup>a</sup>	Yield / %
CH₃(CH₂) <sub>6</sub> CHO	Br	A	67
	Br	В	67
	Cl	А	74
Ph	Br	А	87
	Br	В	79
	Br	А	93
	Br	В	90 (1:1.4) <sup>b</sup>
	Cl	Α	91
CH₃CO(CH₂)₅CH₃	Br	А	85
	Br	В	71
	Cl	Α	94
PhCOMe	Br	А	56
	Br	В	58
	Cl	Α	29
$\frown$	Br	А	99
<∕>=∘	Br	В	91
	Cl	Α	89
PhCOPh	Br	А	46
	Br	В	47
≻€⊃=∘	Br	А	91
	Br	В	72 (1:1) <sup>b</sup>
	Cl	Α	91
PhCHO	Br	A	27

Table	Reaction of XCF <sub>2</sub> COOEt with SmI	2 in the Presence of Aldehyde or Ketone
	X of	

<sup>a</sup> Method A; XCF<sub>2</sub>COOEt (1.0 mmol) and carbonyl compound(2.0 mmol) were used for the reaction, and the yields were determined by <sup>19</sup>F-NMR using PhCF<sub>3</sub> as an internal standard based on XCF<sub>2</sub>COOEt. Method B; reaction was performed using BrCF<sub>2</sub>COOEt (1.0 mmol) and carbonyl compound (0.9 mmol): isolated yield based on carbonyl compound is shown.

<sup>b</sup> Ration of the isomers determined by <sup>19</sup>F-NMR.

effective with BrCF<sub>2</sub>COOEt (reflux in THF for 30 min), and required high temperature (70 °C), longer reaction time (20 h), and higher polar solvent such as DMF.<sup>7</sup> It is, therefore, of particular importance to note that the reaction of inexpensive ClCF<sub>2</sub>COOEt with SmI<sub>2</sub> completed at room temperature within 1 min in THF.<sup>8</sup>

SmI<sub>2</sub> is available from Aldrich Co. Ltd. as a THF solution or easily prepared from samarium powder with I<sub>2</sub> in THF, and easy to handle. Thus, the results described here shows that SmI<sub>2</sub> has high potential to realize a practically useful Reformatsky type reactions to construct  $\alpha, \alpha$ -difluoro-3-hydroxy ester under very mild conditions.

#### Experimental

Starting material BrCF<sub>2</sub>COOEt was obtained from Tokyo Kasei Kogyo Co. Ltd. and purified by distillation prior to use. CICF<sub>2</sub>COOEt was prepared from CICF<sub>2</sub>COOH with EtOH. SmI<sub>2</sub> was prepared from samarium powder and I<sub>2</sub> in THF according to a literature,<sup>9</sup> and used as a THF solution (0.1 mol dm<sup>-3</sup>). The concentration was determined by iodometry prior to use.

Typical Procedure for Reformatsky Reaction of  $BrCF_2COOEt$ using SmI<sub>2</sub> for the Isolation of 2,2-Difluoro-3-hydroxy Ester:  $BrCF_2COOEt$  (1.0 mmol) and 2-octanone (0.9 mmol) in THF was added to a solution of SmI<sub>2</sub> (2.2 mmol) in THF at room temperature under nitrogen. The color of the solution turned from purple to yellow at once, indicating the end of the reaction. After the workup with 1N-HCl, organic products were extracted with ether (3 x 10 mL), and the combined organic layer was washed with water. The solution was dried over MgSO<sub>4</sub>, and then ether and THF were removed. Purification of the residue with gel-permeation chromatography (JAI model LC- 908 liquid chromatograph equipped with two JAIGEL-1H columns) gave corresponding 2, 2-difluoro-3-hydroxy ester (1) in 71% yield.

2,2-Difluoro-3-hydroxy-3-methylnonanoic acid ethyl ester (1): colorless oil; <sup>1</sup>H-NMR(CDCl<sub>3</sub>)  $\delta$  0.89 (t, J=6.8Hz, 3H), 1.30 - 1.47(m, 8H), 1.32 (s, 3H), 1.37 (t, J=7.2Hz, 3H), 1.60 (t, J=8.1Hz, 3H), 2.04 (s, 1H), 4.36 (q, J=7.2Hz, 2H); <sup>13</sup>C-NMR (CDCl<sub>3</sub>)  $\delta$  13.9, 14.0, 19.7, 22.46, 22.52, 29.7, 31.7, 35.2, 62.9, 74.6 (t, J=24Hz), 116.1 (t, J=259Hz), 163.8 (t, J=33.1Hz); <sup>19</sup>F-NMR (CDCl<sub>3</sub>)  $\delta$ (ppm from external CF<sub>3</sub>COOH) -40.4 and -42.4 (ABq, J=253Hz), m/z 253 (M+1), 237, 165; Analysis; C:56.63, H: 9.27%; Calcd for C<sub>12</sub>H<sub>22</sub>F<sub>2</sub>O<sub>3</sub>; C: 57.13, H: 8.79%.

In the reaction of 4-*t*-butylcyclohexanone two stereoisomers of 2,2-difluoro-2-(1'-hydroxy-4'-t-butylcyclohexyl) acetic acid ethyl ester (**2a** and **2b**) were obtained in almost 1:1 ratio, and separated by gel-permeation chromatography.

**2a**: Colorless oil; <sup>1</sup>H-NMR(CDCl<sub>3</sub>)  $\delta$  0.87 (s, 9H), 0.99 (m, 1H), 1.36 (t, J=6.83Hz, 3H), 1.40 - 1.85 (m, 4H), 2.15 (s, 1H), 2.29 - 2.36 (m, 4H), 4.34 (q, J=6.83Hz, 2H); <sup>13</sup>C-NMR(CDCl<sub>3</sub>)  $\delta$  13.9, 21.3, 27.4, 30.2, 32.3, 47.2, 62.8, 73.3 (t, J<sub>CCF</sub>=23.9Hz), 116.0 (t, J<sub>CF</sub>=258Hz), 163.8 (t, J<sub>CCF</sub>=31.2Hz); <sup>19</sup>F-NMR(CDCl<sub>3</sub>)  $\delta$ (ppm from external CF<sub>3</sub>COOH) -43.8 (s, 2F); Found: M<sup>+</sup>, 278.1650, C<sub>14</sub>H<sub>24</sub>F<sub>2</sub>O<sub>3</sub> requires 278.1639.

**2b**: Colorless oil; <sup>1</sup>H-NMR(CDCl<sub>3</sub>)  $\delta$  0.86 (s, 9H), 1.12 (m, 1H), 1.36 (t, J=6.83Hz, 3H), 1.43 - 1.83 (m, 4H), 2.30 - 2.35 (m, 4H), 2.48 (s, 1H), 4.35 (q, J=6.83Hz, 2H); <sup>13</sup>C-NMR(CDCl<sub>3</sub>)  $\delta$  13.9, 21.3, 27.5, 32.3, 33.7, 46.2, 62.9, 72.5 (t, J<sub>CCF</sub>=23.9Hz), 117.4 (t, J<sub>CF</sub>=258Hz), 163.8 (t, J<sub>CCF</sub>=31.2Hz); <sup>19</sup>F-NMR(CDCl<sub>3</sub>)  $\delta$ (ppm from external CF<sub>3</sub>COOH) -36.0 (s, 2F); Found: M<sup>+</sup>, 278.1717, C<sub>14</sub>H<sub>24</sub>F<sub>2</sub>O<sub>3</sub> requires 278.1639.

Similarly, 2-phenylpropionaldehyde gave corresponding two diastereomer **3a** and **3b** in the ratio of 1:1.4. These isomers were also separated by gel-permeation chromatography.

**3a**: Colorless oil; <sup>1</sup>H-NMR(CDCl<sub>3</sub>)  $\delta$  1.32 (t, J=7.33, 3H), 1.41 (d, J=7.32, 3H), 2.38 (s, 1H), 3.17 (m, 1H), 4.24 (m, 1H), 4.25 (q, J=7.33, 2H), 7.25 - 7.34 (m, 5H); <sup>13</sup>C-NMR(CDCl<sub>3</sub>)  $\delta$  13.8, 18.5, 40.5, 63.0, 75.2 (t, J<sub>CCF</sub>=23.9Hz), 114.9 (t, J<sub>CF</sub>=258Hz), 127.3, 128.3, 128.8, 141.3, 163.5 (t, J<sub>CCF</sub>=33.1Hz); <sup>19</sup>F-NMR(CDCl<sub>3</sub>)  $\delta$ (ppm from external CF<sub>3</sub>COOH) -32.0 (d, J<sub>FF</sub>=263Hz, 1F), -47.8 (dd, J<sub>FF</sub>=263Hz, J<sub>HF</sub>=18.3Hz); Found: M<sup>+</sup>, 258.1099, C<sub>13</sub>H<sub>16</sub>F<sub>2</sub>O<sub>3</sub> requires 258.1067.

**3b**: Colorless oil; <sup>1</sup>H-NMR(CDCl<sub>3</sub>)  $\delta$  1.28 (t, J=7.33, 3H), 1.40 (d, J=7.32, 3H), 2.39 (s, 1H), 3.15 (m, 1H), 4.13 (q, J=7.33, 2H), 4.27 (m, 1H), 7.25 - 7.34 (m, 5H); <sup>13</sup>C-NMR(CDCl<sub>3</sub>)  $\delta$  13.8, 16.2, 39.6, 63.0, 74.9 (t, J<sub>CCF</sub>=23.9Hz), 114.7 (t, J<sub>CF</sub>=258Hz), 126.9, 127.9, 128.5, 142.9, 163.6 (t, J<sub>CCF</sub>=33.1Hz); <sup>19</sup>F-NMR(CDCl<sub>3</sub>)  $\delta$ (ppm from external CF<sub>3</sub>COOH) -38.5 (dd, J<sub>FF</sub>=266Hz, J<sub>HF</sub>=9.2Hz, 1F), -43.3 (dd, J<sub>FF</sub>=266Hz, J<sub>HF</sub>=13.8Hz); Found: M<sup>+</sup>, 258.0974, Cl<sub>3</sub>H<sub>16</sub>F<sub>2</sub>O<sub>3</sub> requires 258.1067.

All the other known products shown in Table were characterized by <sup>1</sup>H, <sup>13</sup>C, <sup>19</sup>F-NMR and MS spectra.

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(Received in Japan 20 November 1995)