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## A Novel Reaction of β,β'-Dihydroxy Acids or Esters with Vanadium(V) Trichloride Oxide. New Entry to the Stereoselective Synthesis of α-Fluoro-α,β-unsaturated Acids and Esters

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## Abstract

 $\beta$ , $\beta$ '-Dihydroxy carboxylic acids and esters, readily prepared from dibromofluoroacetate and aldehydes, underwent deoxygenation, followed by elimination of aldehyde by the action of vanadium(V) trichloride oxide at the reflux temperature of chlorobenzene for 1 h to afford the Z isomers of  $\alpha$ -fluoro- $\alpha$ , $\beta$ -unsaturated acids and esters, respectively, in fair to good yields. This reaction provides a new alternative entry to the stereoselective synthesis of such fluoro compounds. © 1998 Elsevier Science Ltd. All rights reserved.

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 $\alpha$ -Hydroxy or  $\beta$ -hydroxy carboxylic acids are known to undergo oxidative decarboxylation [1] or decarboxylation-deoxygenation [2,3], respectively, by the action of vanadium(V) trichloride oxide (VOCl<sub>3</sub>) or its derivatives. Notably, the latter reaction constitutes a direct route to the synthesis of olefins from  $\beta$ -hydroxy carboxylic acids. During the course of our studies on the synthesis and application of  $\alpha$ -fluorinated  $\beta$ -hydroxy carbonyl compounds [4-9], we have found that  $\alpha$ -fluoro- $\beta$ , $\beta$ '-dihydroxy carboxylic acids (1) and esters (2), accessible from dibromofluoroacetate and aldehydes [6], are subject to a novel type of reaction with VOCl<sub>3</sub>, giving  $\alpha$ -fluoro- $\alpha$ , $\beta$ -unsaturated carboxylic acids (3) and esters (4) with Z stereoselectivity.

 $\alpha$ -Fluoro- $\alpha$ , $\beta$ -unsaturated acids and their derivatives are an important class of compounds and are widely used as potent building blocks in organic synthesis, particularly in the preparation of biologically active compounds, such as fluorinated analogues of retinoids [10], pheromones [11], or pyrethroids [12]. Therefore, development of the synthetic methods for these compounds is still required though a number of methods have appeared in the literature [13-23].

This communication discloses the preliminary results of the reactions of 1 or 2 with VOCl<sub>3</sub>,



Table 1

The results of the reaction between  $\beta_i\beta'$ -dihydroxy acids 1 or esters 2 and VOCl<sub>3</sub>

Entry 1	$\beta$ , $\beta$ '-Dihydroxy acid <b>1</b> or ester <b>2</b>			VOCl <sub>3</sub>	Temp.	Time	Yield <sup>a</sup> /%	
		R	R	/equiv.	/°C	/h	of 3 or 4	
	la	Ph	Ph	1	80	6	3a	40
2 <sup>b</sup>	1a	Ph	Ph	1	80	18	_	tr
3°	1a	Ph	Ph	1	120	1	3a	39
4	1a	Ph	Ph	1	refl.	1	3a	48
5	1a	Ph	Ph	2	refl.	1	3a	70
6	1b	p-MeC <sub>6</sub> H <sub>4</sub>	p-MeC <sub>6</sub> H <sub>4</sub>	2	refl.	1	3b	76
7	1c	p-MeOC <sub>6</sub> H <sub>4</sub>	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub>	2	refl.	1	3c	58
8	1d	p-FC <sub>6</sub> H <sub>4</sub>	p-FC <sub>6</sub> H <sub>4</sub>	2	refl.	1	3d	59
9	1e	p-ClC <sub>6</sub> H <sub>4</sub>	p-ClC <sub>6</sub> H <sub>4</sub>	2	refl.	1	3e	58
10	1f	1-Naphthyl	1-Naphthyl	2	refl.	1	3f	75
11	1g	CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub>	CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub>	2	refl.	18	—	0
12	1h	Ph	CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub>	2	refl.	1	3a	55
13	2a	Ph	Ph	2	refl.	1	4a	61
14	2b	p-MeC <sub>6</sub> H <sub>4</sub>	p-MeC <sub>6</sub> H <sub>4</sub>	2	refl.	1	4b	70
15	2c	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub>	p-MeOC <sub>6</sub> H <sub>4</sub>	2	refl.	1	4c	62
16	2d	p-FC <sub>6</sub> H <sub>4</sub>	p-FC <sub>6</sub> H <sub>4</sub>	2	refl.	1	4d	66
17	2e	p-ClC <sub>6</sub> H <sub>4</sub>	p-ClC <sub>6</sub> H <sub>4</sub>	2	refl.	1	4e	47
18	2f	1-Naphthyl	1-Naphthyl	2	refl.	1	4f	58
19	2i	p-ClC <sub>6</sub> H <sub>4</sub>	(CH <sub>3</sub> ) <sub>2</sub> CH	2	refl.	4	4e	49
20	2j	1-Naphthyl	(CH <sub>3</sub> ) <sub>2</sub> CH	2	refl.	4	4f	47

<sup>a</sup> The yields are of pure products isolated by column chromatography.

<sup>b</sup> The reaction was carried out in benzene.

<sup>c</sup> The reaction was performed in *t*-butylbenzene.

providing a new alternative means for the stereoselective synthesis of  $\alpha$ -fluoro- $\alpha$ , $\beta$ -unsaturated acids and esters.

The starting dihydroxy acids 1 and esters 2 were easily prepared according to our previously reported procedure [6]. On treatment of 1a with VOCl<sub>3</sub> (1 equiv.) in chlorobenzene at reflux temperature (ca. 120 °C) for 1 h,  $\alpha$ -fluorocinnamic acid (3a) was obtained in 48% yield (Entry 4). The use of 2 equiv. of VOCl<sub>3</sub> improved the reaction; the hydroxy acid 1a was completely consumed to give 3a in good yield (Entry 5), along with a comparable amount of benzaldehyde. The product 3a was found by careful <sup>19</sup>F NMR (FT) analysis to be comprised of the Z isomer, whose geometry was explicitly assigned on the basis of the magnitude of the vicinal H-F

coupling [24]. Neither reaction using 1 equiv. of VOCl<sub>3</sub> in chlorobenzene (Entry 1) or benzene at 80 °C (Entry 2) nor reaction in t-butylbenzene at 120 °C (Entry 3) provided us with satisfactory results; particularly, the reaction in benzene did not proceed, resulting in the recovery of 1a. Various  $\beta$ ,  $\beta$ '-dihydroxy acids **1b-f** carrying aryl groups underwent the reaction with  $VOCl_3$  (2 equiv.) in chlorobenzene under reflux for 1 h to give the Z isomers of the corresponding  $\alpha$ -fluoro- $\alpha$ ,  $\beta$ -unsaturated acids **3b-f** in fair to good yields (Entries 6-10). The corresponding aromatic aldehydes were also produced in these reactions. Unfortunately. the acid 1g bearing an alkyl group did not entirely participate in this reaction even if the reaction time was prolonged (Entry 11). Of much significance is that the reaction of 1h having aryl and alkyl groups gave **3a**, no 2-fluoro-2-pentenoic acid being formed at all (Entry 12). It should be noted that the present reaction did not lead to the formation of 2-fluoro-1,3-diaryl-2-propen-1-ols, which is presumed from the results of the VOCl<sub>2</sub>-mediated reaction of  $\beta$ -hydroxy acids reported by Meier and Schwartz [2,3].

In a similar way was examined the reaction of  $\beta$ ,  $\beta$ '-dihydroxy esters 2 with VOCl<sub>3</sub>. When diaryl-substituted dihydroxy esters 2a-f were made to react with VOCl<sub>3</sub> (2 equiv.) in chlorobenzene under reflux for 1 h, the corresponding (Z)- $\alpha$ -fluoro- $\alpha$ ,  $\beta$ -unsaturated esters 4a-f were obtained as only one geometrical isomer in fairly good yields (Entries 13-18). The reaction of unsymmetrically substituted esters 2i and 2j with VOCl<sub>3</sub> produced the Z isomers of aryl-substituted  $\alpha$ -fluoro- $\alpha$ ,  $\beta$ -unsaturated esters 4e and 4f (Entries 19 and 20).

The reactions described herein were found to be retarded or inhibited by the addition of a radical scavenger. Thus, on treatment of 1a or 2a with VOCl<sub>3</sub> in the presence of galvinoxyl (0.5 equiv.) in chlorobenzene at reflux temperature for 1 h, the yield of 3a or 4a was lowered to the extent of 38% and 8%, respectively. These findings strongly suggest that the reactions proceed through a radical intermediate, and hence allowed us to deduce the following possible mechanism for the present reaction.



The dihydroxy acid 1 or ester 2 reacts with  $VOCl_3$  to form a vanadate ester species 5 with liberation of hydrogen chloride. The resultant ester 5 undergoes homolytic fission of a C-O bond, where the bond between the aryl-substituted carbon and vanadate ester oxygen can be cleaved preferentially to produce a carbon-centered radical intermediate 6 stabilized by the aryl

substituent. Subsequent collapse of this radical would give rise to the product 3 or 4, together with aldehyde and vanadium dichloride oxide. The Z stereoselectivity observed in the reaction could be attributed to the difference in stabilities between the two conformers 6A and 6B of the radical 6; the conformer 6A, sterically more stable than 6B, may participate exclusively in the reaction to result in the formation of the Z isomer of the product. It should be mentioned that no isomerization between the E and Z isomers of the product occurred under the reaction conditions; if a 71 : 29 mixture of the E and Z isomers of 4a in chlorobenzene was heated to reflux in the presence or absence of VOCl<sub>3</sub> for 1-4 h, the isomer ratio was not altered at all.

In summary, we have demonstrated a novel type of reaction between  $\beta$ ,  $\beta'$ -dihydroxy acids or esters and VOCl<sub>3</sub>, which involves the  $\beta$ -elimination of a hydroxyl group and aldehyde molecule. The present reaction can serve as a new alternative approach to synthesizing  $\alpha$ -fluoro- $\alpha$ ,  $\beta$ -unsaturated acids and esters in a Z stereoselective manner.

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