



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

Takashi Ishihara,* Atsuhiko Shintani, and Hiroki Yamanaka

*Department of Chemistry and Materials Technology, Kyoto Institute of Technology,
Matsugasaki, Sakyo-ku, Kyoto 606-8585, Japan*

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Abstract

β,β' -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 α -fluoro- α,β -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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α -Hydroxy or β -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_3) or its derivatives. Notably, the latter reaction constitutes a direct route to the synthesis of olefins from β -hydroxy carboxylic acids. During the course of our studies on the synthesis and application of α -fluorinated β -hydroxy carbonyl compounds [4-9], we have found that α -fluoro- β,β' -dihydroxy carboxylic acids (**1**) and esters (**2**), accessible from dibromofluoroacetate and aldehydes [6], are subject to a novel type of reaction with VOCl_3 , giving α -fluoro- α,β -unsaturated carboxylic acids (**3**) and esters (**4**) with *Z* stereoselectivity.

α -Fluoro- α,β -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_3 ,

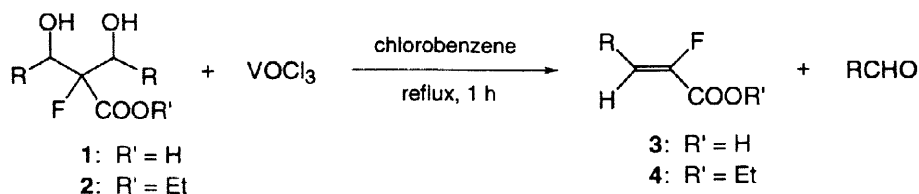


Table 1

The results of the reaction between β,β' -dihydroxy acids **1** or esters **2** and VOCl_3

| Entry | β,β' -Dihydroxy acid 1 or ester 2 | | VOCl_3 /equiv. | Temp. /°C | Time /h | Yield ^a /% | |
|----------------|---|---|---|--------------|------------|-------------------------|--------------|
| | R | R | | | | of 3 or 4 | |
| 1 | 1a | Ph | Ph | 1 | 80 | 6 | 3a 40 |
| 2 ^b | 1a | Ph | Ph | 1 | 80 | 18 | — tr |
| 3 ^c | 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 | <i>p</i> -MeC ₆ H ₄ | <i>p</i> -MeC ₆ H ₄ | 2 | refl. | 1 | 3b 76 |
| 7 | 1c | <i>p</i> -MeOC ₆ H ₄ | <i>p</i> -MeOC ₆ H ₄ | 2 | refl. | 1 | 3c 58 |
| 8 | 1d | <i>p</i> -FC ₆ H ₄ | <i>p</i> -FC ₆ H ₄ | 2 | refl. | 1 | 3d 59 |
| 9 | 1e | <i>p</i> -ClC ₆ H ₄ | <i>p</i> -ClC ₆ H ₄ | 2 | refl. | 1 | 3e 58 |
| 10 | 1f | 1-Naphthyl | 1-Naphthyl | 2 | refl. | 1 | 3f 75 |
| 11 | 1g | CH ₃ CH ₂ CH ₂ | CH ₃ CH ₂ CH ₂ | 2 | refl. | 18 | — 0 |
| 12 | 1h | Ph | CH ₃ CH ₂ CH ₂ | 2 | refl. | 1 | 3a 55 |
| | | | | | | | |
| 13 | 2a | Ph | Ph | 2 | refl. | 1 | 4a 61 |
| 14 | 2b | <i>p</i> -MeC ₆ H ₄ | <i>p</i> -MeC ₆ H ₄ | 2 | refl. | 1 | 4b 70 |
| 15 | 2c | <i>p</i> -MeOC ₆ H ₄ | <i>p</i> -MeOC ₆ H ₄ | 2 | refl. | 1 | 4c 62 |
| 16 | 2d | <i>p</i> -FC ₆ H ₄ | <i>p</i> -FC ₆ H ₄ | 2 | refl. | 1 | 4d 66 |
| 17 | 2e | <i>p</i> -ClC ₆ H ₄ | <i>p</i> -ClC ₆ H ₄ | 2 | refl. | 1 | 4e 47 |
| 18 | 2f | 1-Naphthyl | 1-Naphthyl | 2 | refl. | 1 | 4f 58 |
| 19 | 2i | <i>p</i> -ClC ₆ H ₄ | (CH ₃) ₂ CH | 2 | refl. | 4 | 4e 49 |
| 20 | 2j | 1-Naphthyl | (CH ₃) ₂ CH | 2 | refl. | 4 | 4f 47 |

^a The yields are of pure products isolated by column chromatography.^b The reaction was carried out in benzene.^c The reaction was performed in *t*-butylbenzene.

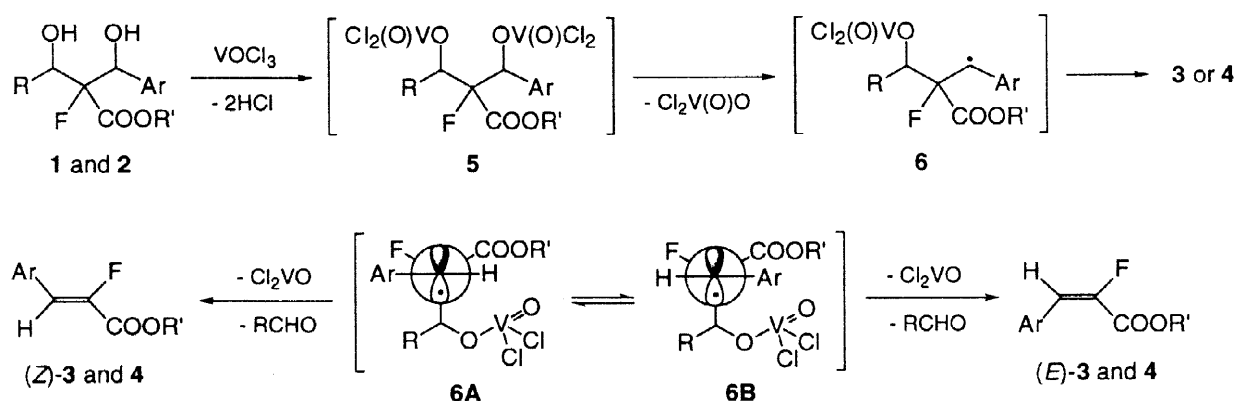
providing a new alternative means for the stereoselective synthesis of α -fluoro- α,β -unsaturated acids and esters.

The starting dihydroxy acids **1** and esters **2** were easily prepared according to our previously reported procedure [6]. On treatment of **1a** with VOCl_3 (1 equiv.) in chlorobenzene at reflux temperature (ca. 120 °C) for 1 h, α -fluorocinnamic acid (**3a**) was obtained in 48% yield (Entry 4). The use of 2 equiv. of VOCl_3 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 ¹⁹F 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_3 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 β,β' -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 α -fluoro- α,β -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_3 -mediated reaction of β -hydroxy acids reported by Meier and Schwartz [2,3].

In a similar way was examined the reaction of β,β' -dihydroxy esters **2** with VOCl_3 . When diaryl-substituted dihydroxy esters **2a-f** were made to react with VOCl_3 (2 equiv.) in chlorobenzene under reflux for 1 h, the corresponding (*Z*)- α -fluoro- α,β -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_3 produced the *Z* isomers of aryl-substituted α -fluoro- α,β -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_3 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_3 for 1-4 h, the isomer ratio was not altered at all.

In summary, we have demonstrated a novel type of reaction between β,β' -dihydroxy acids or esters and VOCl_3 , which involves the β -elimination of a hydroxyl group and aldehyde molecule. The present reaction can serve as a new alternative approach to synthesizing α -fluoro- α,β -unsaturated acids and esters in a *Z* stereoselective manner.

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