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Radical-mediated hydroxytrifluoromethylation of α,β -unsaturated esters

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Abstract—Treatment of α , β -unsaturated esters with trifluoromethyl iodide and triethylborane in the presence of KF and H₂O gave the corresponding hydroxytrifluoromethylated esters.

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The addition reactions of perfluoroalkyl radical to carbon-carbon double bonds are very efficient and versatile for the direct introductions of perfluoroalkyl group to organic molecules,1 but the reactions are mainly limited to electron rich alkenes.² With electron deficient alkenes, the formation of undesired dimeric, telomeric and polymeric products is often observed.³ Recently we reported the chelation-controlled diastereoselective alkyl radical additions to α -methylene- γ -oxycarboxylic acid esters and the origin of stereoselectivity.⁴ As an extension of the radical reactions, we report herein the radical-mediated hydroxytrifluoromethylation of α,β -unsaturated esters 1a-fusing CF₃I and Et₃B in the presence of KF and H₂O.

Initially, we examined the radical reaction of ethyl 2-phenethylpropenoate 1a with CF_3I (Scheme 1). Table 1 summarizes the representative results of the radical reaction under selected conditions. Following the procedure for the alkyl radical addition,⁴ the reaction of **1a** with CF₃I (gaseous, ca. 6 equiv.) was performed in the presence of Et₃B (1 equiv.) and Bu₃SnH (3 equiv.) in anhydrous CH₂Cl₂ at -30°C for 6 h. Work-up with KF and H_2O^5 gave hydroxytrifluoromethylated ester 2a in 61% isolated yield (Table 1, entry 1). Neither trifluoromethylated ester 3 nor iodotrifluoromethylated ester 4^{2b} formed. As it was found that Bu₃SnH did not act as a hydrogen donor, the reaction was performed without the additives (entry 2). But the reaction gave a complex mixture and **2a** was isolated only in 20% yield. The formation of alcohol 2a is probably due to the

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contamination of water during the bubbling of CF₃ gas at -30° C. We next performed the reaction in the presence of H₂O (4 equiv.) and KF (30 equiv.), but without the tin reagent. The reaction gave **2a** in 50% isolated and 90% conversion yields (entry 3). No reaction took place in the absence of the radical initiator Et₃B. The reaction performed without KF gave lower yield (entry

$$\begin{array}{c|c} CF_{3}I \\ Et_{3}B \\ CO_{2}Et \\ 1a \end{array} \begin{array}{c} CF_{3}I \\ Et_{3}B \\ additives \\ solvent \end{array} \begin{array}{c} CF_{3} \\ OH \\ CO_{2}EI \\ 2a \end{array}$$

Scheme 1.

Table 1. Hydroxytrifluoromethylation of 1a with CF₃I^a

Entry	Additive (equiv.)	Solvent	Temp. (°C)	Yield of 2a (%) ^b
1	Bu ₃ SnH (3)	CH ₂ Cl ₂	-30	61
2	_	CH_2Cl_2	rt	20
3	H ₂ O (4), KF (30)	CH_2Cl_2	rt	50 (90)
4	$H_2O(4)$	CH_2Cl_2	rt	25
5	H ₂ O (4), KF (30)	THF	rt	75 (95)
6	H_2O (4), K_2CO_3 (10)	THF	rt	46 (53)

^a For entry 1: **1a** was treated with CF_3I (ca. 6 equiv.), Et_3B (1 equiv.) and Bu_3SnH at $-30^{\circ}C$ and after completion of reaction, the mixture was stirred with KF and H_2O at rt for an additional 3 h. For entry 2: the reaction was performed with CF_3I (ca. 6 equiv.) and Et_3B (1 equiv.). For entries 3, 4 and 6: the reaction was performed similarly to the typical procedure (Ref. 7). For entry 5: see Ref. 7. ^b Isolated yield. Conversion yield in parenthesis.

Keywords: hydroxytrifluoromethylation; α , β -unsaturated esters; radical reaction.

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Table 2. Hydroxytrifluoromethylation of electron deficient alkenes 1b–f with CF_3I



^a Isolated yield. Conversion yield in parenthesis.

^b E/Z ratio of 1c = 2.6:1. Diastereomer ratio of 2c = ca. 40:60. The relative configurations of 2c were not determined.

^c Diastereomer ratio of 2d = ca. 40:60. The relative configurations of 2d were not determined.

^d Diastereomer ratio $(2R^*, 2'R^*)$ -2e: $(2S^*, 2'R^*)$ -2e = ca. 60:40.

^e Diastereomer ratio $(2R^*, 2'R^*)$ -2f: $(2S^*, 2'R^*)$ -2f = ca. 60:40.

4). The use of THF as solvent enhanced the yield of **2a** (75% isolated and 95% conversion yields, entry 5). $K_2CO_3^{6}$ was less effective than KF (entry 6).

We applied subsequently the best reaction conditions⁷ (Table 1, entry 5) to various electron deficient alkenes **1b**-**f** (Table 2). The reaction of ethyl 2-hexylpropenoate **1b** afforded the corresponding hydroxytrifluoromethylated product 2b in 70% yield (entry 1). Nonterminal alkene **1c** was also reacted with trifluoromethyl radical to give 2c despite the radical addition reaction of nonterminal alkenes is in general sluggish (entry 2).8 α -Methylene- γ -lactone 1d⁹ also gave the corresponding hydroxytrifluoromethylated lactone 2d, although the yield was lower (entry 3). However, the addition of electron deficient trifluoromethyl radical was not suitable for the highly electron deficient 2phenethylacrylonitrile⁸ and the starting material was recovered.

The addition of trifluoromethyl radical to γ -methoxy- α methylenecaboxylic acid ester $1e^{4b,d}$ gave the hydroxytrifluoromethylated esters $2e^{10}$ in 76% yield with a poor diastereoselectivity, $(2R^*,2'R^*)$ -2e: $(2S^*,2'R^*)$ -2e = 60:40 (entry 4). The success in the chelation-controlled 1,3-asymmetric induction in the alkyl radical addition to α -methylene- γ -oxycaboxylic acid esters⁴ prompted us to apply the chelation control to the hydroxytrifluoromethylation reaction. However, Lewis acid La(OTf)₃, which is known to coordinate with carbonyl oxygens even in water,¹¹ did not improve the diastereoselectivity (entry 5).¹² The reaction of γ -benzyloxy- α -methylenecarboxylic acid ester $1f^{4b,d}$ also gave hydroxytrifluoromethylated esters $2f^{10}$ in good yield, but with a poor diastereoselectivity (entry 6).

These results mentioned above show that the hydroxytrifluoromethylation reaction proceeded in a radical manner and the hydroxyl group in **2a** arose from water. In fact the reaction of **1a** using $H_2^{18}O$ gave ¹⁸O labeled **2a** (HRMS: calcd for $C_{14}H_{17}F_3^{16}O_2^{18}O$ (M⁺) 292.1240, found 292.1215). The alcohol **2a** was not transformed into ¹⁸O labeled **2a** under radical reaction conditions in the presence of $H_2^{18}O$. These results suggest the hydrolysis of iodide **4** into the alcohol **2a**. A possible reaction pathway for the formation of hydrotrifluoromethylation products is shown in Scheme 2. The addition of trifluoromethyl radical to electron deficient alkenes **A** give the radical intermediate **B**. The subsequent iodineatom transfer reaction may give trifluoromethylated iodide **C**, which is unstable and easily hydrolyzed with water to give hydroxytrifluoromethylated product **D**.

The reaction of 1a with the electron deficient radical derived from ethyl iodoacetate gave alcohol 5 in 71% isolated and 83% conversion yields, but the reaction with ethyl bromoacetate did not give the alcohol because the bromine-atom transfer reaction is slower compared to the iodine-atom transfer reaction.¹³ The result suggests the reaction proceeded through the α iodoester, although the intermediate was not detected in the reaction mixture because of rapid hydrolysis with water. In order to verify the rapid hydrolysis, diethyl 2-iodo-2,4-dimethylpentanedioate (7)¹⁴ and ethyl 2iodo-2-methylpentanoate (8)¹⁵ were allowed to react with KF and water in THF under the conditions similar to those shown in Ref. 7 (Scheme 3). The hydrolysis of iodide 7 bearing an electron-withdrawing ethoxycarbonyl group β to the quaternary carbon atom was completed within 6 h and the corresponding tert-alco-



Scheme 2. Possible reaction pathway.



Scheme 3.

hol 9, analogous to compound 5, was yielded quantitatively. However, the hydrolysis of iodide 8 was slower and only 70% of 8 was converted into the corresponding alcohol 10. The role of KF was found to be the acceleratation of hydrolysis, because without KF the hydrolysis was sluggish.

The conversion of halides to alcohols, via peroxyl radical intermediates, with oxygen and Et_3B has been reported.^{2e,16} In our case, however, the reaction of **1a** with CF₃I performed in the presence of Et_3B and 2 equiv. of molecular oxygen in CH₂Cl₂ gave hydroperoxide **6** in 45% yield together with **2a** (30% yield; see, entry 2 in Table 1). The hydroperoxide **6** was easily reduced to the corresponding alcohol **2a** under H₂-Pd/C conditions. The radical intermediate formed by the addition of trifluoromethyl radical may react with molecular oxygen to give the hydroperoxide **6** (see, **E** in Scheme 2).

In summary, we have reported the first example of the radical-mediated hydroxytrifluoromethylation of α , β -unsaturated esters using trifluoromethyl iodide and triethylborane in the presence of KF and H₂O. The new method would be useful for the synthesis of trifluoromethyl-containing organic compounds.

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