Aldol-Type Self Condensation of α-Halo-α,α-difluoromethyl-ketones by Using the Bimetal Redox System [Cr(III)/Fe]

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Recently the introduction of difluoromethylene functionality into organic compounds has attracted much attention, because compounds containing difluoromethylene-unit such as α,α-difluoroketones and α,α-difluorinated alcohols could be the inhibitors of various enzymatic reactions and also metabolized into more active substances.[1] It has been argued that the difluoromethylene group could be regarded as an isopolar-isosteric replacement for oxygen.[2] Especially α,α-difluoro-β-hydroxy carbonyl compounds are gaining increased interest, because they are successfully applied to the synthesis of fluorine-containing analogues of the biologically important compounds such as sugars, amino acids, fatty acid, and nucleosides.[3] However there are few reports toward the synthesis of α,α-difluoro-β-hydroxy carbonyl compounds, because only limited methods have been available for the synthesis of α,α-difluorocarbonyl compounds.[4] Reformatsky reaction have been used to prepare α,α-difluoro-β-hydroxy carbonyl compounds from the reaction of aldehydedes with α-chloro-α,α-difluoromethylketones[5] and α-bromo-α,α-difluoroacetates.[6] Recently Hu *et al.* reported a synthetic method of introducing CF_2Br_2 into α,β-unsaturated ester such ethyl acrylate using bimetal redox systems, such as the catalytic systems composed of catalytic amounts of chromium(III)chloride hexahydrate and iron powder, or Co(III) and Zn powder.[7] Herein, we wish to report that α,α,γ,γ-tetrafluoro-β-hydroxy ketones can be efficiently synthesized from the aldol type self-condensation of α-halo-α,α-difluoromethylketones *via* the above Hu groups redox system, which is shown below (Scheme 1).

As starting materials, α-bromo or α-iodo-α,α-difluoromethyl ketones (**2**) were prepared from α-chloro-α,α-difluoroacetic acid (**1**) according to the known methods.[8] The reaction[9] of ketone (**2**) with 2.0 equiv. of iron powder and 0.15 equiv of chromium(III) chloride hexahydrate in THF afforded desired α,α,γ,γ-tetrafluoro-β-hydroxy ketone (**3**) in moderate yields as shown in Scheme 1. These results are summarized in Table 1.

α-Iodo-α,α-difluoromethyl ketones such as **2ac**, **2ad** and **2ae** gave slightly higher yields than the corresponding α-bromo-α,α-difluoromethyl ketones. No condensation product was observed with α-chloro-α,α-difluoromethyl ketone.
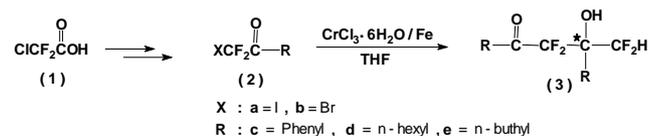
It is also noteworthy that the reaction showed the highest yield when the functional R was n-butyl as shown in Table 1.

We have used either absolute ethanol or dry THF as the reaction solvent, In case of THF, yield was increased by 5-8%. In fact, the products **3** were unexpected derivatives and it is interesting that γ-iodide or γ-bromide of originally expected condensation products (not depicted) was reduced into hydrogen atom under the reaction condition. But trace amount of non-reduced condensation products was detected on GC-Mass of crude products. The products **3** were identified by ^{1}H NMR, ^{13}C NMR, ^{19}F NMR, and Mass Spectra. Two groups of chemical shifts and coupling patterns of fluorine atoms were in ^{19}F NMR spectra. One is for α-fluorines and other for γ-fluorine. Two fluorines of γ-carbon were geminally coupled to ABq type each other at -54 ppm, showing coupling constant of $J_{F-Fgem} > 280$ Hz and each peak was splitted to doublet ($J_{F-Hgem} = 54$ Hz) by coupling with hydrogen of 6.39 ppm. Also two fluorines of α-carbon were coupled to ABq type, representing coupling constant of $J_{F-Fgem} > 280$ Hz at -40 ppm.

In summary, the α,α,γ,γ-tetrafluoro-β-hydroxyketones were efficiently obtained from α-iodo- or α-bromo-α,α-difluoromethyl ketones with the bimetal redox system composed of catalytic amounts of chromium(III)chloride hexahydrate and iron powder *via* aldol-type self condensation.[10]

Experimental Section

^{1}H NMR, ^{13}C NMR and ^{19}F NMR were recorded by a Varian unity plus 300 (300 MHz) spectrometer. All samples were taken in $CDCl_3$ solvent and all chemical shifts were recorded in parts per million downfield (positive) from the standard. ^{19}F NMR spectra are referenced against internal $CFCl_3$. All the mass spectra analyses were performed at 70 eV in the electron impact mode. The IR spectra were

Scheme 1

Table 1. Synthesis of α,α,γ,γ-tetrafluoro-β-hydroxy-ketones

entry	Substrate	X	R	Product	Yield (%)[a]
1	**2ac**	I	Phenyl	**3c**	65
2	**2bc**	Br	Phenyl	**3c**	58
3	**2ad**	I	*n*-Hexyl	**3d**	70
4	**2bc**	Br	*n*-Hexyl	**3d**	63
5	**2ae**	I	*n*-Butyl	**3e**	77
6	**2be**	Br	*n*-Buytl	**3e**	67

[a]Isolated yield.

obtained by a Perkin Elmer ^{16}F-PC spectrometer with CCl_4 solutions.

General synthesis of α,α,γ,γ-tetrafluoro-β-hydroxyketones. A heterogeneous solution of α-iodo or α-bromo-α,α-difluoromethyl ketone derivatives **2** (3.0 mmol), chromium(III) chloride hexahydrate (0.45 mmol), iron powder (6.0 mmol) and dry THF (10 mL) was heated at reflux for 20 hrs. The reaction mixture was cooled at room temperature and poured into water (20 mL). After filtration, extraction with methylene (20 mL), drying with $MgSO_4$, evaporation under reduced pressure, and column chromatography provided **3** as a colorless liquid.

2,2,4,4-Tetrafluoro-1,2-diphenyl-3-hydroxy-1-butanone (3c). ^{19}F NMR (300 MHz, $CDCl_3$): δ -29.3 (d, $J_{F,Fgem}$=295.3 Hz, 1F), -30.7 (d. $J_{F,Fgem}$=295.3 Hz, 1F), -52.5 (dd, $J_{F,Fgem}$=289.9 Hz, $J_{H,Fgem}$=54.2 Hz, 1F), -54.27 (dd, $J_{F,Fgem}$=289.9 Hz, $J_{H,Fgem}$=54.2 Hz, 1F); ^{1}H NMR ($CDCl_3$): δ 7.9 (d. *J*=7.2Hz 2H), 7.6 (m, 4H), 7.4 (m, 4H), 6.4 (t, $J_{H,Fgem}$=54.8 Hz, 1H), 5.3 (s, -OH); ^{13}C NMR (300 MHz, $CDCl_3$): δ 186.3 (t, $J_{C,F}$=25.1 Hz), 135.3 (s), 133.3 (s), 130.9 (s), 130.5 (s), 129.9 (s) 129.8 (s), 129.5 (s), 129.2 (s), 129.1 (s), 129.0 (s), 128.7 (s), 127.5 (s), 114.6 (t, $J_{C,F}$=251.9 Hz), 113.4 (t, *J*=262.4 Hz), 54.1 (m); MS m/z (relative intensity) 312 (M$^+$, 0.01), 261 (1), 207 (3.6), 156 (14), 105 (100), 77 (64); IR 3486 (m, -OH), 2937 (m), 1702 (s, C=O), 1598 (m), 1450 (m), 1280 (m), 1134 (s).

6,6-Difluoro-7-difluoromethyl-7-hydroxy-5-undecanone (3d). ^{19}F NMR (300 MHz, $CDCl_3$): δ -38.9 (d, $J_{F,Fgem}$=281.5 Hz, 1F), -41.1 (d. $J_{F,Fgem}$=281.5 Hz, 1F), -53.0 (dd, $J_{F,Fgem}$=290.70 Hz, $J_{H,Fgem}$=54.8 Hz, 1F), -54.8 (dd, $J_{F,Fgem}$=290.7 Hz, $J_{H,Fgem}$=54.8 Hz, 1F); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.9 (t. $J_{H,Fgem}$=54.7 Hz), 3.6 (s, -OH), 2.8 (t, *J*=7.10 Hz, 2H), 1.9 (t, *J*=8.1 Hz, 2H), 1.6 (q. *J*=7.4 Hz, 2H), 1.5-1.2 (m. 12H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 188.5 (t. *J*=24.2 Hz), 114.9 (t, $J_{C,F}$=248.7 Hz), 113.5(t, $J_{C,F}$=262.4 Hz), 45.4 (m), 37.8 (s), 29.5 (s), 24.4 (s), 23.3 (s), 22.2 (s), 21.9 (s), 13.8 (s); MS m/z (relative intensity) 272 (M$^+$, 0.01), 221 (0.7), 119 (0.7), 103 (1), 85 (100), 57 (54); IR 3464 (s, -OH), 2962 (s), 1740 (s, C=O), 1562 (m), 1404 (m), 1076 (s).

8,8-Difluoro-9-difluoromethyl-9-hydroxy-7-pentadecanone (3e). ^{19}F NMR (300 MHz, $CDCl_3$): δ -38.9 (d, $J_{F,Fgem}$=282.3 Hz, 1F), -41.1 (d, $J_{F,Fgem}$=282.3 Hz, 1F), -53.0 (dd, $J_{F,Fgem}$=289.9 Hz, $J_{H,Fgem}$=54.9 Hz, 1F), -54.8 (dd, $J_{F,Fgem}$=289.9 Hz, $J_{H,Fgem}$=54.9 Hz, 1F); ^{1}H NMR ($CDCl_3$): δ 5.9 (t, $J_{H,Fgem}$=54.7 Hz, 1H), 3.6 (s, -OH), 2.7 (t, *J*=7.0 Hz 2H), 1.8 (t, *J*=8.1 Hz 2H), 1.6-1.1 (m, 22H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 188.6 (t, $J_{C,F}$=24.2 Hz), 114.8 (t, $J_{C,F}$=248.6 Hz), 113.5 (t, $J_{C,F}$=262.3 Hz), 45.9 (m), 38.0 (s), 31.5 (s),

29.8 (s), 29.7 (s), 28.4 (s), 23.0 (s), 22.5 (s), 22.4 (s), 22.3 (s), 21.0 (s), 16.0 (s), 13.9 (s); MS m/z (relative intensity) 328 (M$^+$, 0.01), 277 (0.3), 131 (0.7), 113 (100), 95 (3), 55 (10); IR 3484 (m, -OH), 2930 (m), 1742 (s, C=O), 1464 (m), 1080 (s).

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9. Although the reaction condition were not fully optimized, the yield was not affected by increased amount of chromium chloride or iron powder.

10. The reaction mechanism of these aldol-type self condensation using Cr(III)/Fe bimetal system was not clarified in this study. But it is expected that the rxn presumably involves the formation of radical species from α-iodo or α-bromo-α,α-difluoromethyl ketone **2** by Cr(III)/Fe and the radicals attack another ketone to give an addition product which is followed by *in situ* dehalogenation of the addition product.