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A New, Mild, and Efficient Synthesis of 2,2-Difluoro-3-hydroxyacids through a Selective Haloform Reaction

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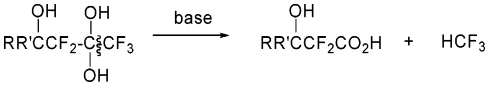
Received September 8, 2005



Long-chain 2,2-difluoro-3-hydroxyacids have been synthesized in a new, straightforward manner by treatment of 4-hydroxy-1,1,1,3,3-pentafluoroalkyl ketones, easily obtained by reaction of pentafluoroenolate **2** with aldehydes and ketones, with base under mild conditions. The reaction sequence is marked by the selective cleavage of the CO−CF_3 bond, as well as the absence of products arising from the alternative CO−CF_2R bond cleavage. The process represents a convenient approach for the synthesis of 2,2-difluoro-3-hydroxyacids, as it is short, provides good to excellent yields under mild conditions, and uses hexafluoro-2-propanol, a very cheap reagent, as the fluorine source.

Fluoroorganic chemistry has garnered great interest in the past few decades owing to the potential of fluorine to act as a hydrogen atom or hydroxyl group mimic. The small size (1.47 Å) of fluorine, as well as the similarity of its van der Waals radius with respect to that of hydrogen (1.20 Å), make it an ideal hydrogen or hydroxyl group (1.40 Å) substitute in bioactive compounds in terms of steric requirements at a receptor site.[1] In addition, the high electronegativity of fluorine (4.0 on the Pauling scale) and the high C−F bond energy (116 kcal·mol^{-1}) imply a significant increase of metabolic, oxidative, and thermal stability of the corresponding fluorinated compounds.[2] These special properties of fluorine have been exploited for the development of new and effective biochemical tools as well as agrochemical, medicinal, and therapeutic agents,[3] particularly in the field of enzymatic inhibition.[4] Particularly attractive are 2,2-difluoro-3-hydroxyacids, which are versatile intermediates for the preparation of a variety of bioactive materials, such as difluorinated gingerol, a potent inhibitor of prostaglandin biosynthesis,[5] chiral 2,2-difluorocitrate as inhibitors of rat liver ATP citrate lyase and porcine heart aconitase[6] or yeast mitochondria,[7] difluorostatine peptides as potent and specific renin inhibitors,[8] proteolysis inhibitors[9] or ferroelectric liquid crystals,[10] among others. Although a number of procedures have been developed to prepare 2,2-difluoro-3-hydroxyacids,[5,11] new, efficient methods of preparation from cheap, easily available fluorinated materials are always desirable. Herein is reported a practical, straightforward, and high-yielding method to obtain 2,2-difluoro-3-hydroxyacids from hexafluoro-2-propanol, a readily available starting material.

In the course of our research on the inhibition of pheromone catabolism in insects by fluorinated derivatives,[12] we discovered that treatment of compound **3a**, easily available from hexafluoro-2-propanol according to the procedure of Nakai,[13,14] with NaH in THF led to the formation of hydroxyacid **4a** in 70% yield (Scheme 1). This unprecedented reaction involves the *selective* cleavage of the CO−CF_3 bond to produce 2,2-difluoro-3-hydroxyacids and fluoroform.

The selectivity is remarkable as, on the basis of the expected small bond strength differences between the CO−CF_3 and CO−CF_2R bonds, cleavage of the CO−CF_2R bond to give difluoromethyl carbinol and trifluoroacetic acid (Scheme 2) would also be expected.

However, none of the latter products were detected, a fact that was very recently rationalized by us using DFT

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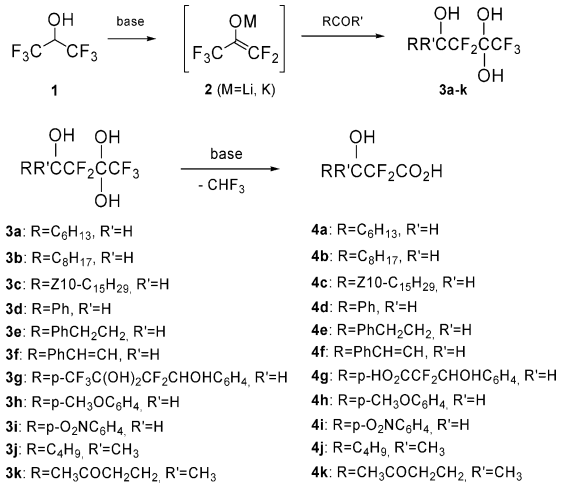
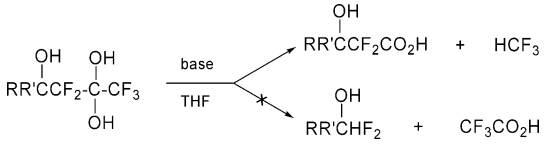
10.1021/jo0518856 CCC: $30.25
Published on Web 11/16/2005

SCHEME 1



SCHEME 2



(B3LYP) calculations of the two possible C−C bond cleavage modes of 1,1,1,3,3-pentafluoro-4-hydroxypentan-2-one as model compound in the gas phase.[15] Although loss of the trifluoromethyl group has been known since 1943,[16] very few examples of loss of fluoroform from trifluoromethyl carbinols have been reported,[17] and no case has been found from pentafluorinated substrates such as **3a**−**k**. To study the scope and limitations of this reaction, a variety of hydroxy pentafluoroketones **3a**−**k** were obtained by reaction of the Li or K pentafluoroenolate **2** of hexafluoro-2-propanol **1** with carbonyl compounds (see Supporting Information). Among these compounds, only acetophenone and benzene-1,4-dicarboxaldehyde were poor substrates toward enolate **2**. The enolates were quantitatively prepared from hexafluoro-2-propanol by treatment with 2 equiv of *n*-BuLi in THF or by sequential reaction with 1 equiv of KH followed by 1 equiv of *n*-BuLi.[13] Compounds **3a**−**k** were obtained in good yields as mixtures of the hydrate and the hemiacetalic forms and in no case was the presence of the free ketone detected (Chart 1).

When hydroxy pentafluoroketones **3a**−**k** were subjected to treatment with NaH (5 equiv) in THF or 5 N aqueous NaOH (20 equiv) in THF at room temperature, 2,2-difluoro-3-hydroxyacids **4a**−**k** were obtained in good to excellent yields (Scheme 1, Table 1).

The process appears to be independent of the presence of other functional groups in the molecule and can occur in pure organic solvent (THF) or in an aqueous-solvent environment. In addition, the starting fluorinated ketones can be used as mixtures of the keto and hydrate forms without first being dehydrated. As expected, when two $COCF_3$ groups (in the form of hydrates) are present in the molecule, such as in bis-pentafluoroketone **3g**, cleavage occurred at both groups, yielding bis-difluoroacid **4g**. Compound **4k** was obtained exclusively in its hemiacetalic form, as indicated by the presence of the hemiacetalic carbon at 113.9 ppm in the ^{13}C NMR and the absence of the CH_3CO group in IR and ^{13}C NMR.

In summary, a new procedure to obtain 3-hydroxy-2,2-difluoroacids in very good yields has been developed. The synthetic route of these versatile and very useful fluorinated materials is short and efficient, requires only mild conditions, and uses hexafluoro-2-propanol, a cheap and readily available fluorine source.

CHART 1. General Hydrate (A) and Hemiacetalic (B) Forms of 3-Hydroxy-2,2-difluoroalkyl Trifluoromethyl Ketones 3a−k

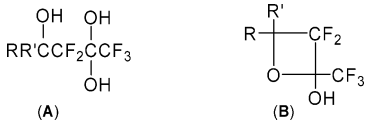


TABLE 1. Base-Promoted Conversion of 3-Hydroxy-2,2-difluoroalkyl Trifluoromethyl Ketones 3a−k into 2,2-Difluoro-3-hydroxyacids 4a−k[a]

entry	substrate	base[b]	solvent	time (h)	product	yield[c] (%)
1	**3a**	NaH	THF	4	**4a**	70
2	**3a**	NaOH (1 N)	THF/H_2O	27	**4a**	80[d]
3	**3a**	NaOH	THF/H_2O	17	**4a**	89
4	**3b**	NaOH	THF/H_2O	23	**4b**	83
5	**3b**	NaH	THF	3	**4b**	87
6	**3c**	NaOH	THF/H_2O	16	**4c**	92
7	**3d**	NaOH	THF/H_2O	22	**4d**	69
8	**3e**	NaOH	THF/H_2O	17	**4e**	89
9	**3f**	NaOH	THF/H_2O	15.5	**4f**	79
10	**3g**	NaOH	THF/H_2O	22	**4g**	90
11	**3h**	NaOH	THF/H_2O	17	**4h**	86
12	**3i**	NaOH	THF/H_2O	21	**4i**	84
13	**3j**	NaOH	THF/H_2O	22	**4j**	81
14	**3k**	NaOH	THF/H_2O	21	**4k**	84

[a] All reactions were conducted at room temperature. [b] NaH (5 equiv) and 5 N aq NaOH (20 equiv) were used as base, except for substrate **3a** in entry 2. [c] Isolated yields. [d] Yield based on ^{19}F NMR.

Experimental Section

General Procedure for Preparation of 3-Hydroxy-2,2-difluoroalkyl trifluoromethyl Ketones 3a−k. 4-Hydroxy-1,1,1,3,3-pentafluorodecan-2-one (3a) as Representative Example. In a dry, two-neck round-bottomed flask was placed hexafluoro-2-propanol (2 g, 11.9 mmol), recently distilled over anhydrous $MgSO_4$, in anhydrous THF (20 mL) under Ar. The mixture was cooled to −40 °C, at which point a 1.49 M solution of *n*-BuLi in hexane (16 mL, 23.8 mmol) was slowly added with stirring. The reaction was then stirred for 1 h at room temperature. The mixture was again cooled to −40 °C, a solution of recently distilled heptanal (1.8 mL, 13.1 mmol) in THF (5 mL) was added, and the mixture was then stirred at room temperature for 16 h. The solvent was removed, and the residue was taken up in ether (3 × 25 mL), washed with brine, and dried ($MgSO_4$). The solvent was evaporated, and the residue was purified by column chromatography over SiO_2 with a mixture of hexane/Et_2O 70:30, affording compound **3a** in its hydrate form

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(2.48 g, 79% yield). IR (film) ν: 3370, 2959, 2932, 2862, 1468, 1208, 1164, 1121, 1075 cm^{-1}. ^1H NMR (300 MHz) δ: 5.8 (bs, 1H), 4.32 (dd, $J_1 = 21.6$ Hz, $J_2 = 10.2$ Hz, 1H), 3.9 (bs, 1H), 2.3 (bs, 1H), 1.87−1.54 (dm, 2H), 1.30 (bs, 8H), 0.89 (t, $J = 6.9$ Hz, 3H) ppm. ^{19}F NMR (282 MHz) δ: −81.8 (dd, $J_1 = 13.2$ Hz, $J_2 = 9.87$ Hz, 3F), −120.5 (dq, $J_1 = 267$ Hz, $J_2 = 13.2$ Hz, 1F), −132.0 (dm, $J_1 = 267$ Hz, 1F) ppm. ^{13}C NMR (75 MHz) δ: 121.2 (q, $J = 286$ Hz), 116.2 (t, $J = 257$ Hz), 93.0 (m), 71.8 (dd, $J_1 = 31.4$ Hz, $J_2 = 24.3$ Hz), 31.5, 28.9, 28.6, 24.8, 22.5, 13.8 ppm. MS (EI) *m/z* (%): 244 ($M^{\oplus} - H_2O$, 0.48), 229 (1), 115 (38), 97 (100), 69 (95), 57 (50), 55 (53), 43 (71), 41 (74). HRMS calcd for $C_{10}H_{13}OF_5$ [$M^{\oplus} - H_2O$]: 244.0886. Found: 244.0892.

General Procedure for Preparation of 2,2-Difluoro-3-hydroxyacids 4a−k by Reaction of Ketones 3a−k with NaH. 2,2-Difluoro-3-hydroxynonanoic Acid (4a) as Representative Example. In a dry, three-neck round-bottomed flask was placed a solution of the hydrated form of compound **3a** (0.2 g, 0.71 mmol) in anhydrous THF (10 mL) under Ar. An oil dispersion of NaH (60%, 143 mg, 3.56 mmol), previously washed with anhydrous pentane (3 × 5 mL), was then added, and the suspension was stirred for 4 h at room temperature. The resulting mixture was then poured over 1 N HCl (10 mL,) and the solvent was removed. The residue was extracted with Et_2O (3 × 20 mL), washed with water, and dried ($MgSO_4$), and the solvent was removed. The residue was purified by column chromatography on SiO_2 using a mixture of hexane/Et_2O 1:1, to obtain pure **4a** (104 mg, 70% yield). Mp = 55−57 °C. IR (film) ν: 3440, 2957, 2930, 2860, 1758, 1467, 1206, 1120, 1088 cm^{-1}. ^1H NMR (300 MHz) δ: 6.9 (bs, 2H), 4.0 (m, 1H), 1.75−1.50 (dm, 2H), 1.27 (bs, 8H), 0.88 (t, $J = 6.9$ Hz, 3H) ppm. ^{19}F NMR (282 MHz) δ: −114.5 (dd, $J_1 = 262$ Hz, $J_2 = 6$ Hz, 1F), −125.0 (dd, $J_1 = 262$ Hz, $J_2 = 16.6$ Hz, 1F) ppm. ^{13}C NMR (75 MHz) δ: 166.5 (dd, $J_1 = 33$ Hz, $J_2 = 32$ Hz), 114.5 (dd $J_1 = 255$ Hz, $J_2 = 252$ Hz), 71.8 (dd, $J_1 = 28$ Hz, $J_2 = 26$ Hz), 31.5, 28.8, 28.4, 25.0, 22.5, 13.9 ppm. Anal. Calcd for $C_9H_{16}O_3F_2$: C, 51.42; H, 7.67; F, 18.07. Found: C, 51.49; H, 7.75; F, 17.94.

General Procedure for Preparation of 2,2-Difluoro-3-hydroxyacids 4a−k by Reaction of Ketones 3a−k with NaOH as Base. In a three-neck round-bottomed flask was placed a solution of the hydrated form of compound **3a** (105 mg, 0.37 mmol) in THF (0.75 mL). A solution of NaOH (300 mg, 7.49 mmol) in H_2O (0.75 mL) was then added, and the mixture was stirred for 17 h. The reaction mixture was poured over 1 N HCl (10 mL), and the solvent was removed. The mixture was extracted with Et_2O (3 × 20 mL), washed with H_2O, and dried ($MgSO_4$). After removal of the solvent, the residue was purified on SiO_2 using a mixture of hexane/Et_2O 1:1. The acid **4a** was obtained in 89% yield (69 mg).

Acknowledgment. The authors gratefully acknowledge MEC for a predoctoral fellowship to O.J. and CICYT (projects AGL 2003-06599-C02-01, PTR1995-0656-OP) and Generalitat de Catalunya (2001SGR-00342) for financial support.

Supporting Information Available: Scope of the reaction of fluoroenolate **2** (M = Li) with carbonyl compounds, and spectroscopic data of compounds **3b−k** and **4b−k**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0518856