Synthesis of fluoroalkyl-containing β-hydroxyketones by reduction of the corresponding β-diketone derivatives

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The regioselective synthesis of fluoroalkyl-containing β-hydroxyketones by the reduction of the salts of the corresponding β-diketones with $LiAlH_4$ was proposed. This is the sole method for the synthesis of β-hydroxyketones with two fluoroalkyl substituents.

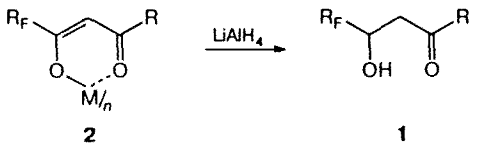
Key words: salts and chelates of fluoroalkyl-containing β-diketones, fluoroalkyl-containing β-hydroxyketones; regioselective reduction.

Fluorine-containing β-hydroxyketones (**1**), unlike their nonfluorinated analogs, are stable to dehydration and serve as synthons for the preparation of different classes of fluorine-containing compounds.[1,2] The main method for their synthesis is the condensation of methyl ketones with fluorinated aldehydes, which are not easily accessible and readily undergo hydration and polymerization.[1,3] The present work is devoted to the search for alternative methods for the synthesis of hydroxyketones **1** based on the accessible fluoroalkyl-containing β-diketones.

It is known that hydrogenation of trifluoroacetylacetone on Raney nickel affords both 1,3-diol and 1,1,1-trifluoro-4-hydroxypentane-2-one.[4] Fluorinated diketones are reduced to 1,3-diols under the action of $NaBH_4$.[5] Earlier chemo- and enantioselective enzymic reduction of trifluoroacetylacetone to the corresponding hydroxyketone was reported.[6] However, these methods are either complex or inefficient.

We have for the first time showed that Li-salts (**2**), as well as Zn-, Mg-, and Al-chelates of β-diketones **2**, are reduced to hydroxyketones **1** in 24—73 % yields with $LiAlH_4$ (Table 1, Scheme 1). The ammonium salts and Cu- and Co-chelates **2** do not afford the corresponding hydrohyketones **1** under similar conditions (see Table 1).

Scheme 1



With R = pyrid-3-yl, the reduction practically does not occur in the traditional solvent, Et_2O. This may be due to the low solubility of both the initial Li-salt and the complex of $LiAlH_4$ with the hydroxyketone **1** formed. The replacement of Et_2O by THF allows one to avoid this difficulty and to obtain for the first time the pyridine-containing hydroxyketone **1** (R_F = CF_3) (see Table 1), which was impossible to synthesize by the condensation of 3-acetylpyridine with trifluoroacetaldehyde, since the latter undergoes polymerization under the action of a pyridine base.

Among all the methods studied by us, only the reduction of Li-salts and Al-chelates **2** is of synthetic value (see Table 1).

Table 1. Yields and melting points of hydroxyketones obtained by reduction β-diketone chelates **2**

R_F	R	M	*n*	Yield (%)	M.p./°C
CF_3	Ph	Li	1	70[a], 74[b]	78—79
CF_3	Ph	Zn	2	28[a]	—
CF_3	4-ClC_6H_4	Li	1	49[a], 62[b]	85—87
CF_3	4-MeOC_6H_4	Li	1	54[a]	103—104
CF_3	4-MeC_6H_4	Li	1	73[a]	96
CF_3	$4\text{-NO}_2C_6H_4$	Li	1	30[a]	98—100
CF_3	3-Py	Li	1	50[a]	135—137
$H(CF_2)_2$	$H(CF_2)_2$	Al	3	68[a]	73—74
C_3F_7	Ph	Li	1	51[b]	61—62
$H(CF_2)_4$	Ph	Li	1	67[b]	89—90
$H(CF_2)_4$	$H(CF_2)_4$	Al	3	72[a]	93—94
C_4F_9	Ph	Li	1	64[a], 60[b]	86—87
C_4F_9	Ph	Co	2	0[a]	—
C_4F_9	Ph	Cu	2	0[a]	—
C_4F_9	Ph	Mg	2	24[a]	—
C_4F_9	Ph	NH_4	1	0[a]	—
$H(CF_2)_6$	Ph	Li	1	39[b]	75—76
C_6F_{13}	Ph	Li	1	65[b]	91—92

[a] Obtained from β-diketone chelate.
[b] Obtained by the Claisen condensation—reduction method.

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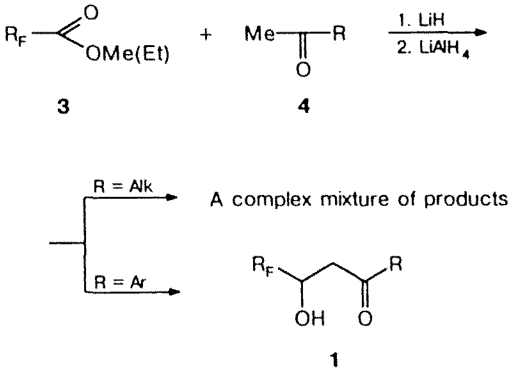
It is noteworthy that the reduction of Al-chelates **2** allows one to obtain hydroxyketones **1** with two fluorinated substituents, which cannot be synthesized by other methods.

With R = Ar, compounds **1** can only be obtained in high yields by reduction of pure Li-salts **2** (see Table 1). With R = Alk, the formation of small amounts of hydroxyketones (according to GLC), which cannot be isolated preparatively, is observed.

We have shown that Li-salts **2** can be obtained directly in the course of Claisen condensation of fluorocarboxylates (**3**) with methyl ketones (**4**) and that they can be reduced with $LiAlH_4$ without isolation and purification (Scheme 2). In this case, LiH should be used instead of the traditional condensation agents (RONa, $NaNH_2$, NaH, or BF_3). If the reaction mixture is treated by the traditional method for Claisen condensation, the corresponding β-diketone can be isolated.

High yields (39—74 %) of products **1** can be achieved only in the case of aryl methyl ketones **4** (see Table 1). The product of the reduction of the CO group and reductive debromination was obtained from ketone **4** (R = 4-BrC_6H_4) by Scheme 2.

Scheme 2



Thus, the methods discussed are efficient only for the preparation of aryl-containing products **1**. The condensation of fluorocarboxylates with alkyl methyl ketones (acetone, pinacoline, *etc.*) followed by reduction affords complex mixtures of products, in which the target compounds **1** can only be observed using GLC by comparison with known samples.

Experimental

^1H NMR spectra were recorded on a Tesla BS-567A spectrometer (100 MHz) with $SiMe_4$ as the internal standard. IR spectra were obtained on a Specord IR-75 instrument in Vaseline oil for solid samples and in thin layers for liquids. GLC analysis was carried out on a LKhM-8MD chromatograph with catharometer as the detector and helium as the carrier gas (2 m×3 mm steel column, 5 % SE-30 on Chromaton N-AW-DMCS). Authentic samples were synthesized by the known methods.[1] TLC control was carried out on Silufol UV-254 plates, products were detected using UV light and $KMnO_4$ and 2,4-dinitrophenylhydrazine solutions.

Reduction of Li-salts and chelates 2. General procedure. $LiAlH_4$ (0.5 mol) was added in portions to a solution of salt or chelate **2** (1.0 mol) in abs. ether with stirring and cooling to 0 °C. The reaction was monitored by TLC. Water and a 20 % HCl solution were added until the solid precipitate was dissolved, the solution was extracted with ether, the extracts were dried with anhydrous $MgSO_4$, the ether was evaporated, and the residue was crystallized from hexane.

Below are the data for the compounds, which have not been described earlier and which cannot be prepared by the known procedure.[1]

1,1,2,2,6,6,7,7-Octafluoro-5-hydroxyheptan-3-one. The yield was 68 %. IR (Vaseline oil), ν/cm^{-1}: 3400 (OH); 1750 (CO). ^1H NMR ($CDCl_3$), δ: 2.90 (m, 1 H, OH); 3.14 (m, 2 H, CH_2); 4.56 (m, 1 H, CH); 5.96 and 6.10 (both t, 2 H, 2 HCF_2, J = 52 Hz).

4,4,4-Trifluoro-3-hydroxy-1-(pyrid-3-yl)butan-1-one. The yield was 50 %. IR (Vaseline oil), ν/cm^{-1}: 3360 (OH), 1680 (CO). ^1H NMR ($CDCl_3$), δ: 3.98 (m, 2 H, CH_2); 4.78 (m, 1 H, CH); 5.48 (m, 1 H, OH); 7.55, 8.36, 8.79, 9.20 (all m, 4 H, Py).

Synthesis of hydroxyketones 1 by the Claisen condensation—reduction method. General procedure. A mixture of polyfluorocarboxylate (1.2 mol) and methyl ketone (1.0 mol) in abs. ether was added dropwise to a suspension of finely powdered LiH (2.1 mol) in abs. ether with stirring at ~20 °C. The reaction was not allowed to proceed vigorously. The mixture was then refluxed till the completion of the reaction (according to TLC) and the mixture, which solidified on cooling, was diluted with abs. ether. The reduction was carried out by the procedure described above.

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