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A NEW EFFICIENT METHOD FOR THE GENERATION OF F-ALKYL KETONE METAL ENOLATES BY USING COPPER(II) BROMIDE-LITHIUM ALUMINIUM HYDRIDE REAGENT AND THEIR ALDOL REACTION WITH CARBONYL COMPOUNDS[1]

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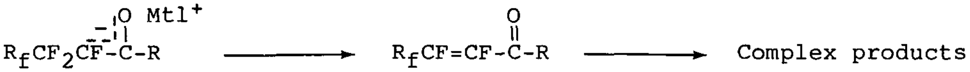
Abstract: 1-Substituted F-1-alkenyl phosphates, readily prepared from F-alkyl ketones and sodium diethyl phosphite, were treated with copper(II) bromide-lithium aluminium hydride reagent at -30 °C to generate *in situ* F-alkyl ketone aluminium enolates, which underwent the aldol reaction with various aldehydes to give the corresponding α-fluoro-α-F-alkyl β-hydroxy ketones in fairly good to excellent yields.

The aldol reaction is one of the most useful and fundamental reactions in the synthesis of a variety of naturally occurring substances. A lot of methods for effecting this transformation have so far appeared in the literature.[2] In contrast, there are not so many studies directed towards the generation and synthetic applications of fluorinated enolates,[3] particularly those bearing an F-alkyl substituent at the carbanionic center of the enolate. Such circumstances seem to be induced by the well-recognized notion that these types of fluorinated enolates like **1** are much too unstable to use successfully and decompose with a loss of β-fluorine atom to form complex products.



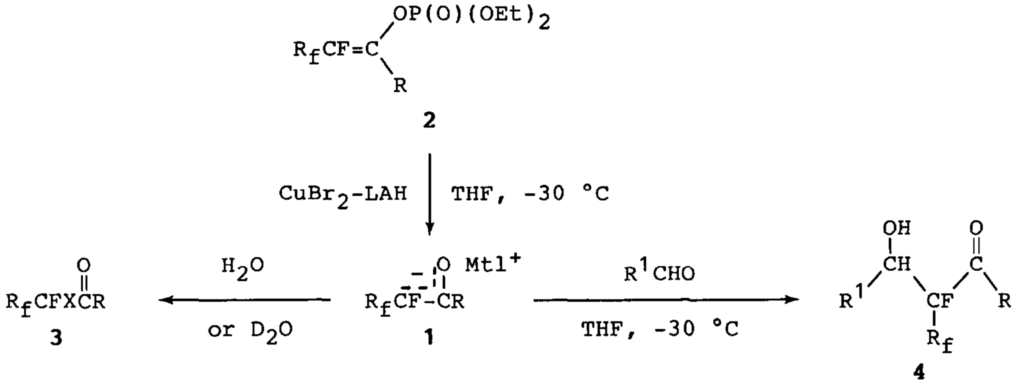
$$R_fCF_2\overset{-}{C}F-\overset{O\ Mtl^+}{\overset{|}{C}}-R \longrightarrow R_fCF=CF-\overset{O}{\overset{\|}{C}}-R \longrightarrow \text{Complex products}$$

1

During the course of our efforts to develop new methods and precursors for generating F-alkylated ketone enolates,[4] we have found that 1-substituted-F-1-alkenyl phosphates (**2**), easily accessible in high yields from F-alkyl ketones and sodium diethyl phosphite, can be employed as a promising precursor of the enolate.

This communication describes a novel efficient method for the generation of F-alkyl ketone metal enolates (**1**) by using copper(II) bromide-lithium aluminium hydride reagent, as well as their aldol reaction with various carbonyl compounds leading to α-fluoro-α-F-alkyl β-hydroxy ketones (**4**) in fairly good to excellent yields.

When fluorinated enol phosphate (**2**)[5] was treated in tetrahydrofuran (THF) at -30 °C with the reagent[6] which had been prepared in THF at -30 °C by the reaction between copper(II) bromide and lithium aluminium hydride (LAH), followed by quenching with water or deuterium oxide, the corresponding protonated or deuteriated ketone (**3**)[7] (X = H or D) was obtained in a yield of 66-96%. Even use of a zinc(II) chloride- or tin(II) chloride-LAH reagent, instead of copper(II) bromide-LAH reagent, afforded 1*H*-*F*-alkyl ketone **3** quantitatively. Of more significance is that the reagent prepared from bromine (2 equiv) and LAH (2 equiv) was also effective for the reaction. These findings strongly suggest that the present reaction involves an intermediary ketone enolate (**1**) and that the metal countercation (Mtl^+) of **1** is an aluminium metal species, though its actual structure is not clear at present.



The above-mentioned enolates (**1**) were expected to react with other electrophiles. In fact, the reaction of enol phosphate (**2**) with copper(II) bromide-LAH reagent, followed by treatment with a variety of carbonyl compounds at -30 °C, provided the corresponding α-fluoro-α-*F*-alkyl β-hydroxy ketones (**4**).[7] Table I summarizes the yields and isomeric ratios of **4**.

Aliphatic, aromatic, and α,β-unsaturated aldehydes readily underwent the aldol reaction with **1** to give **4** in fairly good to excellent yields, whereas the reaction of ketones did not take place at all in spite of the reaction time and temperature being varied. The addition of a Lewis acid, such as boron(III) fluoride diethyl etherate, chlorodiethylaluminium, or titanium(IV) chloride, resulted in a decrease of the yield of **4**. In place of copper(II) bromide, copper(I) chloride, bromide, or iodide could also be used, though a large amount (4 equiv) of it was needed for allowing the desired reaction to proceed cleanly.

The isomer ratios in the products (**4**) were 0.4-3.7 : 1,[8] some of which could be determined as a diastereomeric (erythro to threo) ratio.[9] These values are suggestive of the erythro isomer of **4** being formed in slight preference to the threo isomer. It is noted, however, that exact evaluation for the stereochemistry of the reaction should await further investigations, since an isomeric mixture of **2** was employed in the present study.

The general procedure for the aldol reaction is as follows: A solution

Table I. Aldol Reaction of Fluorinated Enol Phosphates **2** with Aldehydes

Entry	R_f	R	Aldehyde	Yield[a] (%) of **4**	Isomer ratio[b]
1	CF_3	$CH_3(CH_2)_5$	CH_3CH_2CHO	70	0.7:1
2			$CH_3(CH_2)_2CHO$	70	0.8:1
3			(E)-$CH_3CH{=}CHCHO$	39	1:1
4	CF_3CF_2	$CH_3(CH_2)_5$	CH_3CH_2CHO	58	0.7:1
5			$CH_3(CH_2)_2CHO$	49	1.8:1
6			$(CH_3)_2CHCHO$	51	0.4:1
7			$(CH_3)_3CCHO$	tr	-
8			$CH_3(CH_2)_5CHO$	51[c]	1.1:1
9			(E)-$CH_3CH{=}CHCHO$	66	1.3:1[d]
10			C_6H_5CHO	51[c]	1.5:1[d]
11	CF_3CF_2	c-C_6H_{11}	$CH_3(CH_2)_2CHO$	72	0.7:1
12			(E)-$CH_3CH{=}C(CH_3)CHO$	38	0.8:1[e]
13	CF_3CF_2	C_6H_5	$CH_3(CH_2)_2CHO$	49	0.7:1
14			$(CH_3)_2CHCHO$	37	3.7:1
15			(E)-$CH_3CH{=}CHCHO$	34	0.7:1
16	$CF_3(CF_2)_5$	$CH_3(CH_2)_2$	CH_3CH_2CHO	84	0.8:1[e]

a) The yields refer to pure isolated products, unless otherwise cited. b) The values were measured by ^{19}F NMR and represent the ratio of the lower- to higher-field peaks due to the α-methine fluorine in an isomeric mixture of **4**. c) Determined by ^{19}F NMR. d) Erythro : threo ratio.[9] e) Threo : erythro ratio.[9]

of LAH (2 equiv) in THF was slowly added to a well-stirred solution of anhydrous copper(II) bromide (2 equiv) in THF at -30 °C under argon. To the resultant mixture, after 30 min, was added a solution of enol phosphate **2** in THF and the whole mixture was stirred for 3 h at the same temperature. An aldehyde (4-5 equiv) was then added dropwise to the reaction mixture. After stirring for 10 h at -30 °C, the reaction was quenched with an aqueous NH_4Cl-HCl solution, followed by extraction with diethyl ether, drying over anhydrous Na_2SO_4, and evaporation of the solvent. The residue was chromatographed on silica gel to give an analytically pure product **4**, whose isomeric ratio listed in Table I was measured by ^{19}F NMR before isolation.

References and Notes

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5. The starting enol phosphates **2** were obtained as a mixture of geometrical isomers in 70-80% isolated yields by the treatment of F-alkyl ketones with sodium diethyl phosphite in THF at -10 to 0 °C.
6. The copper(I) iodide-LAH combination has been used as a reagent for the conjugate reduction of enones. See, E. C. Ashby and J. J. Lin, Tetrahedron Lett., **1975**, 4453; Idem, ibid., **1976**, 3865; E. C. Ashby, J. J. Lin, and R. Kovar, J. Org. Chem., **41**, 1939 (1976); T. Tsuda, T. Fujii, K. Kawasaki, and T. Saegusa, J. Chem. Soc., Chem. Commun., **1980**, 1013.
7. The spectroscopic (IR, MS, ^{1}H and ^{19}F NMR) and analytical data pertaining to all products reported herein were fully consistent with the assigned structures.
8. See footnote (b) in Table I.
9. The stereochemical assignment to erythro and threo isomers was tentatively made from the analogy of tendency in coupling constants between α-fluorine and β-hydrogen of **4** with that observed[10] in coupling constants between α- and β-hydrogen of β-hydroxy ketones.
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