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PRELIMINARY NOTE

Highly Effective Dephosphorylation of F-1-Alkenyl Phosphates with Copper Halide-Lithium Aluminium Hydride Reagent: A New Access to 1-Hydryl-F-alkyl Ketones from F-Alkyl Ketones*

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SUMMARY

1-Substituted F-1-alkenyl phosphates, readily available from F-alkyl ketones and diethyl phosphite, undergo the dephosphorylation by the action of copper(I) or copper(II) bromide and lithium aluminium hydride at -78 °C followed by hydrolysis to give the corresponding 1-hydryl-F-alkyl ketones in good to excellent yields.

Our attention has been focused on the chemistry and synthetic applications of fluorine-containing carbonyl compounds [1-11], which are an important subject in organic synthesis as well as in organofluorine chemistry. In the course of our studies to explore the reaction between fluorinated ketones and organophosphorus compounds [4], we found that F-alkyl ketones smoothly reacted with sodium diethyl phosphite to give 1-substituted F-1-alkenyl phosphates in high yields. These fluorinated enol phosphates are expected to be a potent precursor for the access to both F-1-alkenyl ketones and α-F-alkylated ketone enolates.

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* Dedicated to Emeritus Professor Teiichi Ando on the occasion of his 65th birthday.

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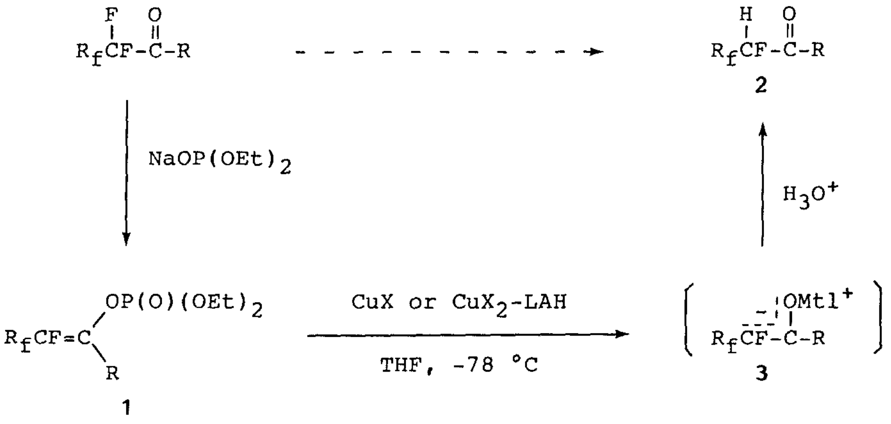
Taking this expectation in mind, we have examined the reaction of F-1-alkenyl phosphates (1) with a variety of aluminium reagents, and have found that the reagent derived from a metal salt and lithium aluminium hydride can effect the selective cleavage of the enol oxygen-phosphorus bond in **1** at low temperature to result in the generation of a transient α-F-alkyl-α-fluoro ketone enolate (**3**).

This preliminary note deals with the reaction of enol phosphates **1** with a copper(I) or copper(II) salt-lithium aluminium hydride reagent, followed by hydrolysis, leading to 1-hydryl-F-alkyl ketones (**2**). The present reaction is the first example for the indirect replacement of fluorine α to a carbonyl function with a hydrogen, as depicted in Scheme 1.



Scheme 1

The reaction was performed in the following manner. A solution of lithium aluminium hydride (LAH) (2 equiv.) in anhydrous tetrahydrofuran (THF) was gradually added to a stirred solution of copper(II) bromide (2 equiv.) in THF at -78 °C under an argon atmosphere. To the resultant mixture, after stirring for 30 min at the same temperature, was added a solution of enol phosphate **1** in THF and then the whole was stirred for 4.5 h at -78 °C. The reaction mixture was poured into a 6N HCl-ice mixture, followed by extraction with ether. The ethereal extracts were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Silica-gel column chromatography of the residue gave analytically pure 1-hydryl-F-alkyl ketone (2).[†] The results of the reaction are summarized in Table 1.

Among the salts examined, copper(I) or copper(II) bromide was the most efficient for the reaction, though the former salt (4 equiv.) was employed in twice the molar quantity of the latter. Other copper salts such as copper(I) chloride and iodide [12] did not allow the reaction to proceed cleanly. The reagent prepared from zinc chloride and LAH was comparably used for the present reaction; the desired product **2** was afforded in a 65% yield (Run 4). It was also found that when enol phosphate **1** was treated with the reagent prepared from bromine and LAH at -78 °C, the corresponding 1-hydryl-F-alkyl ketone (**2**) was obtained in a 61% yield (Run 5). These facts strongly suggest that a metal species generated in situ from the salt and LAH is free from the metal part of the salt and an actual metal species is dihydridoaluminium halide, H_2AlX.

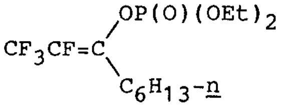
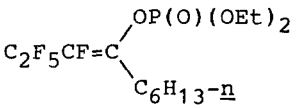
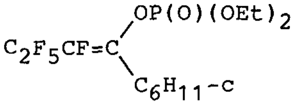
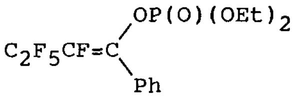
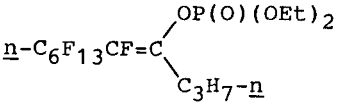
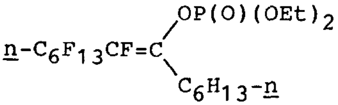
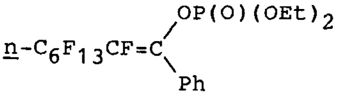
The reaction of **1** with copper(II) bromide-LAH reagent followed by hydrolysis with deuterium oxide furnished good yields of 1-deuteryl-F-alkyl ketones, $R_fCFDCOR$. Even use of lithium aluminium deuteride, instead of LAH, did not produce the deuteriated products at all. These findings show that an α-F-alkyl-α-fluoro ketone aluminium enolate (3) (Mtl = AlL_n) is formed during the reaction.

A variety of enol phosphates **1** readily underwent the dephosphorylation by the action of copper(I) or copper(II) bromide-LAH reagent at -78 °C followed by hydrolysis to give **2** in good to excellent yields, no by-products being formed in any amounts. As Table 1 shows, this reaction can serve as an efficient method for the reduction of α-fluorine [13] in F-alkyl ketones to lead to 1-hydryl-F-alkyl ketones (2), since the starting compounds **1** are available from F-alkyl ketones. To be noted, moreover, is that the reaction described here is characteristic of fluorinated enol phosphates: A fluorine-free enol phosphate such as 1-n-propyl-1-butenyl phosphate failed to react with copper(II) bromide-LAH reagent, resulting in its quantitative recovery.

[†] All the products were fully characterized on the basis of their spectral (IR, MS, ^1H and ^{19}F NMR) and analytical data.

TABLE 1

Efficient Conversion of Fluorinated Enol Phosphates **1** into 1-Hydryl-F-alkyl Ketones **2**

Run	Enol phosphate **1**	Metal salt	Product **2**	Yield %[a]
1	 $CF_3CF{=}C\begin{array}{l}\diagup OP(O)(OEt)_2\\ \diagdown C_6H_{13}\text{-}\underline{n}\end{array}$	$CuBr_2$	$CF_3\text{-}CFHCOC_6H_{13}\text{-}\underline{n}$	91
2	 $C_2F_5CF{=}C\begin{array}{l}\diagup OP(O)(OEt)_2\\ \diagdown C_6H_{13}\text{-}\underline{n}\end{array}$	$CuBr_2$	$C_2F_5\text{-}CFHCOC_6H_{13}\text{-}\underline{n}$	72
3		CuBr[b]		72
4		$ZnCl_2$[c]		65
5		–[d]		61
6	 $C_2F_5CF{=}C\begin{array}{l}\diagup OP(O)(OEt)_2\\ \diagdown C_6H_{11}\text{-}c\end{array}$	$CuBr_2$	$C_2F_5\text{-}CFHCOC_6H_{11}\text{-}c$	86
7	 $C_2F_5CF{=}C\begin{array}{l}\diagup OP(O)(OEt)_2\\ \diagdown Ph\end{array}$	$CuBr_2$	$C_2F_5\text{-}CFHCOPh$	82
8		CuBr[b]		66
9	 $\underline{n}\text{-}C_6F_{13}CF{=}C\begin{array}{l}\diagup OP(O)(OEt)_2\\ \diagdown C_3H_7\text{-}\underline{n}\end{array}$	$CuBr_2$	$\underline{n}\text{-}C_6F_{13}\text{-}CFHCOC_3H_7\text{-}\underline{n}$	96
10	 $\underline{n}\text{-}C_6F_{13}CF{=}C\begin{array}{l}\diagup OP(O)(OEt)_2\\ \diagdown C_6H_{13}\text{-}\underline{n}\end{array}$	$CuBr_2$	$\underline{n}\text{-}C_6F_{13}\text{-}CFHCOC_6H_{13}\text{-}\underline{n}$	62
11	 $\underline{n}\text{-}C_6F_{13}CF{=}C\begin{array}{l}\diagup OP(O)(OEt)_2\\ \diagdown Ph\end{array}$	$CuBr_2$	$\underline{n}\text{-}C_6F_{13}\text{-}CFHCOPh$	79

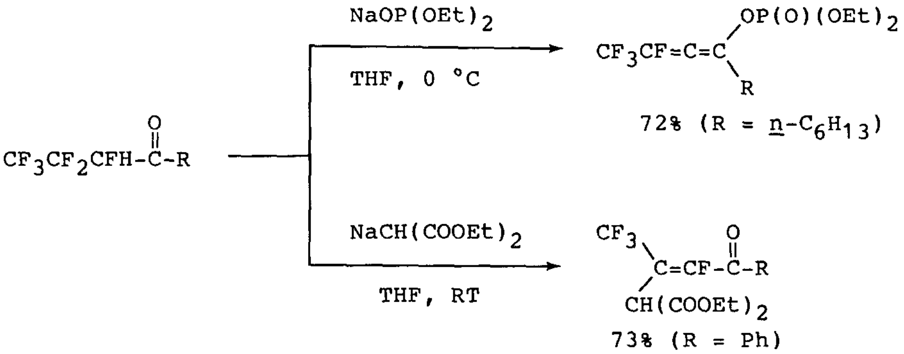
[a] Yields refer to pure isolated products.

[b] The reagent was prepared by the treatment of LAH (2 equiv.) with copper(I) bromide (4 equiv.).

[c] Tetramethylethylenediamine complex (2 equiv.) was used.

[d] The reagent prepared at -78 °C from LAH (2 equiv.) with bromine (2 equiv.) was employed.

Above-obtained ketones 2 are useful and versatile compounds in organic synthesis [14]. Thus, ketone 2 was allowed to react with a nucleophile, such as sodium diethyl phosphite or sodium diethyl malonate, to give the corresponding allenic enol phosphate or 2-(diethylmalono)-F-1-alkenyl ketone, respectively, in the yield shown in Scheme 2.



Scheme 2

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