CHEMISTRY LETTERS, pp. 1621-1622, 1987.

A Convenient Synthesis of Fluorine-Containing Highly-Substituted Furans through New Fluoride Ion-Catalyzed Reaction of 1-Alkyl-*F*-1-alkenyl Phosphates

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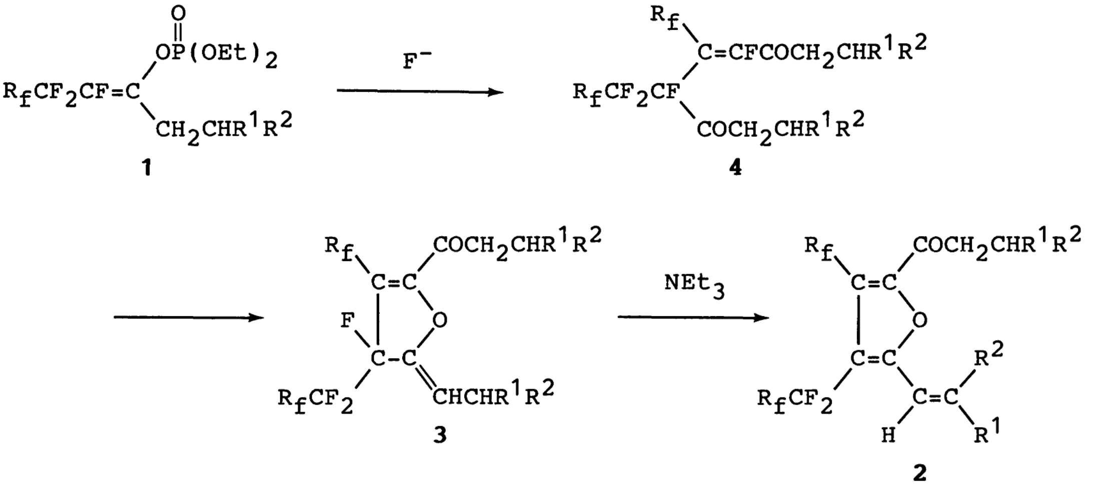
1-Alkyl-*F*-1-alkenyl phosphates, easily prepared from alkyl *F*-alkyl ketones and sodium diethyl phosphite, underwent the dephosphorylation followed by cyclocondensation in the presence of a fluoride ion catalyst and triethylamine at ambient temperature to give 3,4-di-*F*-alkylated furan derivatives in moderate to good yields.

Polysubstituted furans are important starting materials for synthesizing a variety of compounds of pharmacological interest.1) In our studies to develop synthetic utility of fluorine-containing enol phosphates and related compounds,2) we have found that fluoride ion effectively cleaves3) the enol oxygen-phosphorus bond in *F*-alkylated enol phosphates to generate *F*-alkyl ketone enolates and/or *F*-1-alkenyl ketones. This communication describes a new simple synthesis of 3,4-di-*F*-alkylated furan derivatives (2) *via* the unique type of reaction of 1-alkyl-*F*-1-alkenyl phosphates (1) catalyzed by fluoride ion.



When an enol phosphate 1 was treated with a catalytic amount (20 mol%) of fluoride ion and triethylamine (NEt_3) (5 equiv.) at room temperature for 1-5 d, the corresponding 3,4-di-*F*-alkyl-substituted furan (2) was obtained in moderate to good yield. Among the fluoride ion catalysts examined, such as tetrabutylammonium fluoride (TBAF), potassium fluoride, and cesium fluoride, TBAF was the most efficient for the reaction. Tetrahydrofuran (THF) gave more satisfactory results than other solvents such as acetonitrile and dichloromethane. Table 1

Table 1. Synthesis of **2** or **3** by TBAF-catalyzed reaction of **1**[a)]

Enol phosphate			Yield/%[b)] of	
R_f	R^1	R^2	**2**	**3**
CF_3	Et	H	65	48
	Bu	H	69	56
	i-Pr	H	62	46[c)]
	Me	Me	31[c,d)]	44[c)]
$CF_3(CF_2)_4$	Me	H	45	25
	Bu	H	48[d)]	-

a) Products **2** and **3** were fully characterized on the basis of their spectroscopic (IR, MS, ^{1}H and ^{19}F NMR spectra) and analytical data. b) Isolated yield, unless otherwise cited. c) Determined by ^{19}F NMR. d) Reactions were conducted at reflux temperature of THF.

summarizes the results of the reaction of several enol phosphates **1**.

The reaction of enol phosphates derived from *F*-alkyl phenyl ketones resulted in the generation of the corresponding *F*-1-alkenyl phenyl ketones, no condensation products (*e.g.*, **4**) being formed; diethyl 1-phenyl-*F*-1-butenyl phosphate was treated with TBAF and NEt_3 under the same reaction conditions, followed by addition of sodium salt of diethyl malonate (1 equiv.), to give 2-(diethylmalono)-*F*-1-propenyl phenyl ketone in 70% yield.

It was also found that the reaction of **1** with TBAF (20 mol%) in the absence of NEt_3 afforded 2-alkylidene-2,3-dihydrofuran derivatives (**3**) in yields such as listed in Table 1. The compounds **3** could be transformed quantitatively to the furans **2** by treatment with NEt_3 at room temperature. These facts suggest that **3** is an intermediate in the reaction of **1** leading to **2**. A possible mechanism for the reaction is shown in the Scheme. Thus, the enol phosphate **1** reacts with TBAF to generate transient *F*-alkyl ketone enolate (R_fCF_2CFCOR), some of which is converted to *F*-1-alkenyl ketone by a loss of β-fluorine atom. The ketone enolate adds to the resulting α,β-unsaturated ketone in a conjugative manner to afford the intermediate **4**, which may cyclize intramolecularly to **3**. It is possible that the basicity of fluoride ion[4)] plays an important role in this cyclization step. The compound **3** undergoes the 1,4-elimination of hydrogen fluoride by the action of NEt_3 to give the final product **2**.

The reaction described herein provides a new convenient access to fluorine-containing polysubstituted furans, which are difficult to prepare by other methods.

References

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(Received May 20, 1987)