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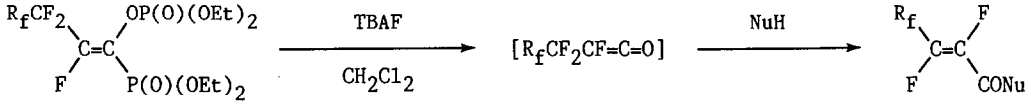
A NOVEL REACTION OF 1-PHOSPHONYLOXY-F-1-ALKENEPHOSPHONATES: HIGHLY EFFECTIVE METHOD FOR THE SYNTHESIS OF α,β-UNSATURATED F-CARBOXYLIC ACID DERIVATIVES

Takashi Ishihara,* Yasuhiro Yamasaki, and Teiichi Ando
Department of Industrial Chemistry, Faculty of Engineering,
Kyoto University, Yoshida, Kyoto 606, Japan

Abstract: 1-Phosphonyloxy-F-1-alkenephosphonates, easily prepared from F-alkanoic acid chlorides and triethyl phosphite, undergo a unique fluoride ion-catalyzed reaction with primary and secondary amines or alcohols to afford the corresponding α,β-unsaturated F-carboxylic acid derivatives in excellent yields, along with diethyl fluorophosphate and phosphite.

α,β-Unsaturated carboxylic acid derivatives are one of the most valuable compounds in organic synthesis and a variety of methods have been developed so far for their preparation. There have been reported, however, very few methods which are effective for preparing perfluorinated analogues,[1] and they are still generally difficult to obtain.

This communication deals with a new fluoride ion-catalyzed reaction of 1-phosphonyloxy-F-1-alkenephosphonate[2] with amines or alcohols, providing a simple, efficient method generally applicable for the synthesis of α,β-unsaturated F-carboxylic acid derivatives.



1 **2**

The reaction was performed in the following manner. To a solution of a primary or secondary amine (1.0 equiv) or an alcohol (1.5 equiv) and tetrabutylammonium fluoride (TBAF) (10-30 mol%, 1M in tetrahydrofuran) in anhydrous CH_2Cl_2 was added 1-phosphonyloxy-F-1-alkenephosphonate (**1**) at 0°C. The mixture was efficiently stirred at ambient temperature for 2 h. Quenching of the reaction with water followed by extraction (Et_2O), drying (Na_2SO_4), concentration *in vacuo*, and distillation or column chromatography on silica gel gave analytically pure product (**2**).[3] The results of the reaction are summarized in Table I.

Cesium fluoride could also be used instead of TBAF as a source of fluoride ion though an equimolar amount was needed for completion of the reaction. Products derived from secondary amines, *i.e.*, N,N-disubstituted carboxamides (**2**, Nu=NR_2) were readily converted to the corresponding free acid[3] (**2**, Nu=OH) on silica-gel column chromatography.

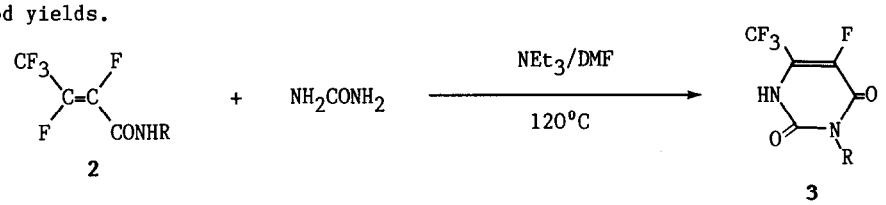
Monitoring the reaction by use of ^{19}F and ^{31}P NMR showed that both diethyl fluorophosphate and phosphite were concurrently produced as the reaction proceeded. In almost all reactions, trace amounts of 1H-F-alkanecarboxylic acid derivatives[3] were detected by ^{19}F NMR, together with **2**. These findings strongly suggest the formation of F-alkylfluoroketene intermediates in the present reaction.[4]

Table I. Synthesis of α,β-Unsaturated F-Carboxylic Acid Derivatives **2**

R_f	Nu	Yield (%)	E/Z[a]
CF_3	$NHCH_2(CH_2)_6CH_3$	91	79/21
	NH-c-C_6H_{11}	84	80/20
	$NHCH_2Ph$	94	83/17
	$NHCH_2(CH_2)_2OH$	73	73/27
	$N(CH(CH_3)_2)_2$	80	80/20
	OCH_2CH_3	90[b]	82/18
$CF_3(CF_2)_3CF_2$	$NHCH_2Ph$	89	99/1
	$NHCH_2CH{=}CH_2$	83	99/1
	$N(CH(CH_3)_2)_2$	83	95/5
	OCH_2CH_3	97[b]	99/1
$CF_3(CF_2)_5CF_2$	$NHCH_2CH_2CH_3$	88	100/0
	$NHCH_2Ph$	94	99/1
	OCH_2CH_3	77[b]	99/1

a) Determined by ^{19}F NMR analysis. b) An excess amount (1.5 equiv) of alcohol was used.

Above-obtained carboxamides **2** could be employed to synthesize fluorinated pyrimidinones, one of the biologically most interesting heterocyclic compounds:[5] Treatment of **2** (R_f=CF_3) with urea and triethylamine in dimethylformamide at 120°C for 4 d gave the corresponding **3**[3] in good yields.



2 **3**

R=n-Oct (55%); R=$PhCH_2$ (60%); R=c-Hex (55%)

References and Notes

1. H.M. Hudlicky, "Chemistry of Organic Fluorine Compounds," Halstead Press, 1976; T. Nguyen, M. Rubinstein, and C. Wakselman, J. Fluorine Chem., **11**, 573 (1978).
2. For the preparation of **1** and its synthetic applications, see: T. Ishihara, T. Maekawa, and T. Ando, Tetrahedron Lett., **24**, 4229 (1983); Idem, ibid., **25**, 1377 (1984); T. Ishihara, Y. Yamasaki, and T. Ando, ibid., **26**, 79 (1985); T. Ishihara, T. Maekawa, and T. Ando, ibid., **27**, 357 (1986).
3. All products were fully characterized on the basis of their spectral (IR, mass, ^1H and ^{19}F NMR) and analytical data.
4. The details of the reaction mechanism will be discussed in a full paper.
5. I. Kumadaki, J. Synth. Org. Chem. Jpn., **42**, 786 (1984); H. Yoshioka, C. Takayama, and N. Matsuo, ibid., **42**, 809 (1984); T. Fuchikami, A. Yamanouchi, and I. Ojima, Synthesis, **1984**, 766; I. Ikeda, Y. Kogame, and M. Okahara, J. Org. Chem., **50**, 3640 (1985).

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