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A New Effective and Convenient Route to Fluorinated Nitrogen Heterocyclic Compounds by the Use of Enol Phosphates Derived from F-Alkyl Ketones[1)]

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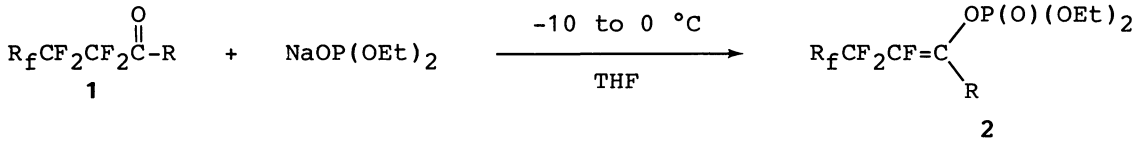
The treatment of F-alkyl ketones with sodium diethyl phosphite in tetrahydrofuran at -10 to 0 °C gave high yields of 1-substituted F-1-alkenyl phosphates, which readily reacted with amidine or hydrazine derivatives at room temperature to afford the corresponding fluorinated pyrimidines or pyrazoles, respectively, in good to excellent yields.

Pyrimidines are a typical class of drugs and have been developed for use as the antimalarial, antibiotic, anticancer, herbicidal, or fungicidal agent. These compounds also frequently exhibit striking differences in their biological activities with their only small structural changes.[2)] In close connection with such circumstances, much effort has been made to exploit novel methods or synthetic intermediates for introducing a fluoro or F-alkyl substituent to organic molecules, particularly those of biological interest.[3)]

In our continuing studies[4)] to develop new general methods for the synthesis of fluorinated heterocyclic compounds, we have found that 1-substituted F-1-alkenyl phosphates, easily available from F-alkyl ketones, can be employed as potent precursors for synthesizing a variety of fluorine-containing pyrimidine and pyrazole derivatives in high yields.



To a solution of sodium diethyl phosphite, generated by the reaction of diethyl phosphite (1 equiv.) with sodium hydride (1 equiv.) in tetrahydrofuran (THF), was dropwise added F-alkyl ketone (**1**)[5)] under argon at -10 °C. This mixture was stirred for 2-3 h at -10 to 0 °C, and then the reaction was quenched with aqueous solution of ammonium chloride. A usual workup followed by column chromatography on silica gel afforded 1-substituted F-1-alkenyl phosphate (**2**)[6)] as a mixture of two geometrical isomers in good yield such as shown in Table 1. Diethyl ether was also used as the solvent (Entries 1, 6, 8, 13, and 14), except for the reaction of aryl F-alkyl ketones (**1**, R = aryl); only use of THF made the

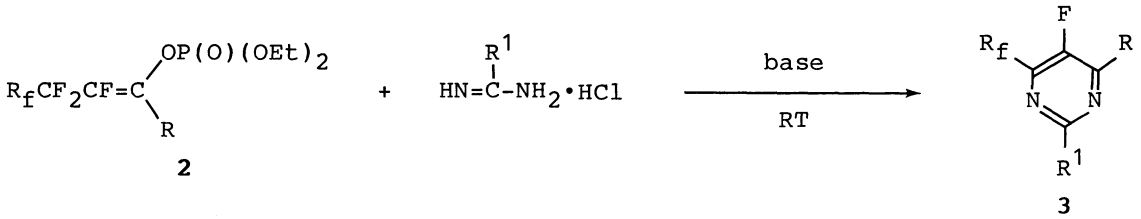
Table 1. Preparation of 1-Substituted E-1-Alkenyl Phosphates 2

Entry	R_f	R	Yield[a]/% of 2
1	F	$CH_3(CH_2)_5$	89[b]
2		Ph	92
3	CF_3	CH_3	67
4		$CH_3(CH_2)_3$	92
5		$(CH_3)_2CHCH_2$	73
6		$CH_2=CH(CH_2)_2$	87[b]
7		$(CH_3)_2CH(CH_2)_2$	72
8		$CH_3(CH_2)_5$	88[83[b]]
9		cyclo-C_6H_{11}	76
10		Ph	79
11		p-$CH_3OC_6H_4$	73
12	$CF_3(CF_2)_4$	$CH_3(CH_2)_2$	80
13		$CH_2=CH(CH_2)_2$	75[b]
14		$CH_3(CH_2)_5$	88[86[b]]
15		Ph	69

a) The yields are of pure isolated products. b) Diethyl ether was employed as the solvent.

reaction of **1** (R = aryl) proceed cleanly (Entries 2, 10, 11, and 15). Of much importance is that either a longer reaction time or higher temperature must be avoided in order to obtain a high yield of **2**, because fluoride ion liberated in the reaction can react further with the product **2**[4c] to result in the formation of many complex products.

When the above-obtained enol phosphate (**2**) was allowed to react with amidine hydrochloride (4 equiv.) in the presence of an appropriate base (4 equiv.) in THF or aqueous THF for 3-12 h at room temperature, 4-alkyl-6-E-alkyl-5-fluoropyrimidine (**3**)[6] was produced in good to excellent yield. The results of the reaction are summarized in Table 2, together with the melting points of **3**.



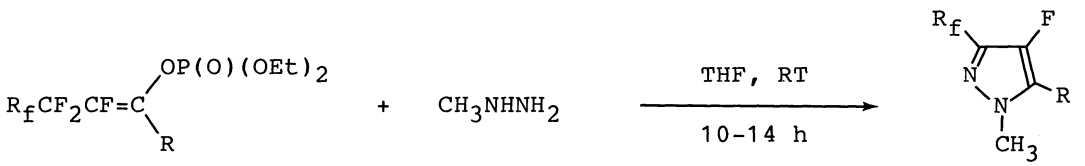
A variety of amidine salts such as formamidine, acetamidine, benzamidine, and guanidine hydrochloride participated well in the reaction. The presence of a base was necessary to generate free amidine molecule from the salt. Among the bases examined, sodium hydride was the most widely usable for this purpose. It should be noted, however, that sodium methoxide (Entry 4), potassium carbonate (Entries 6 and 14), or potassium hydroxide (Entries 8 and 16) was recommended for

Table 2. Synthesis of Fluorinated Pyrimidines 3 from Enol Phosphates 2

Entry	R_f	R	R^1	Base	Yield[a]/% of 3	Mp of 3 °C
1	CF_3	CH_3	NH_2	NaH	64[b,c]	103.1-105.2
2	CF_3	$CH_3(CH_2)_5$	H	NaH	88	
3			CH_3	NaH	90	
4			CH_3	CH_3ONa	94[d]	
5			Ph	NaH	79	
6			Ph	K_2CO_3	61[d,e]	
7			NH_2	NaH	83[b]	33.8-35.9
8			NH_2	KOH	61[d,e]	33.8-35.9
9	CF_3	cyclo-C_6H_{11}	CH_3	NaH	76	
10			Ph	NaH	56	79.1-80.0
11	CF_3	Ph	H	NaH	66	43.2-44.0
12			CH_3	NaH	70	
13			Ph	NaH	76	79.2-80.6
14			Ph	K_2CO_3	79[d,e]	79.2-80.6
15			NH_2	NaH	93	124.4-125.2
16			NH_2	KOH	69[d,e]	124.4-125.2
17	$CF_3(CF_2)_4$	$CH_3(CH_2)_2$	H	NaH	50	

a) The yields refer to pure isolated products, unless otherwise cited. b) Determined by ^{19}F NMR using α,α,α-trifluorotoluene. c) The reaction was conducted in N,N-dimethylformamide. d) The reaction was carried out in a large scale. e) Aqueous THF was used as the solvent.

large-scale preparations, where the choice of them was strongly dependent on the nature of amidine salt employed. The data in Table 2 clearly demonstrate the generality of the reaction. Furthermore, the reaction procedure is extremely simple and the yields of products are good. Thus, the present reaction can serve as a new practical and effective route to regiospecifically fluorinated pyrimidines **3**, which are difficult to obtain by other methods.[7] Of great significance is that the enol phosphates **2**[8] act as synthetic equivalents to F-1-alkenyl ketones ($R_fCF=CFCOR$) in the reaction, since the latter compounds are not easily accessible.[9]



2 **4**

$R_f = CF_3$, $R = CH_3(CH_2)_5$	91%
$R_f = CF_3$, $R = Ph$	82%
$R_f = CF_3$, $R = cyclo\text{-}C_6H_{11}$	90%
$R_f = CF_3(CF_2)_4$, $R = CH_3(CH_2)_2$	90%

It was also found that the treatment of **2** with methylhydrazine (2 equiv.) in THF at room temperature gave the corresponding F-alkylated pyrazoles (**4**)[6] in almost quantitative yields, as depicted above.

Further studies on the synthetic and biological applications[10] of compounds **2**, **3**, and **4** are in progress and will be disclosed in due course.

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2) G.H. Hitchings and J.J. Burchall, Adv. Enzymol., 27, 417 (1965); B. Roth and C.C. Cheng, Prog. Med. Chem., 19, 270 (1982).

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5) The ketones **1** were prepared in good yields from F-alkanoic acids and Grignard reagents with a slight modification of the reported method. See: R. A. Moore and R. Levine, J. Org. Chem., 29, 1439 (1964).

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7) Y.L. Sing and L.F. Lee, J. Org. Chem., 50, 4642 (1985); A. Kreutzberger and M. Sellheim, J. Fluorine Chem., 27, 203 (1985); Y. Inouye, K. Tezuka, W. Takeda, and S. Sugai, ibid., 35, 275 (1987); K. Tanaka, T. Suzuki, S. Maeno, and K. Mitsuhashi, Bull. Chem. Soc. Jpn., 60, 4480 (1987).

8) For using **2** as precursors of F-alkylated ketone enolates, see: M. Kuroboshi, Y. Okada, T. Ishihara, and T. Ando, Tetrahedron Lett., 28, 3501 (1987).

9) For the method for the synthesis of certain F-1-alkenyl ketones, see: P. Moreau, N. Redwane, and A. Commeyras, Bull. Soc. Chim. Fr., 1984, II-117; D. J. Burton and S.W. Hansen, J. Am. Chem. Soc., 108, 4229 (1986).

10) The 5-fluoro substituent in **3** was found to be replaced readily with some nucleophiles: Treatment of **3** (R_f = CF_3, R = hexyl, R^1 = methyl) with sodium methoxide or 2,2,2-trifluoroethoxide gave 5-methoxy- (73%) or 5-(2,2,2-trifluoroethoxy)-substituted pyrimidine (46%), respectively. Some of the new compounds obtained herein exhibited interesting biological activities.

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