CHEMISTRY LETTERS, pp. 1191-1194, 1989.

Dephosphorylation of 1-Substituted F-1-Alkenyl Phosphates with Diisobutylaluminium Hydride. A New Highly Efficient Method for Generating F-Alkyl Ketone Aluminium(III) Enolates

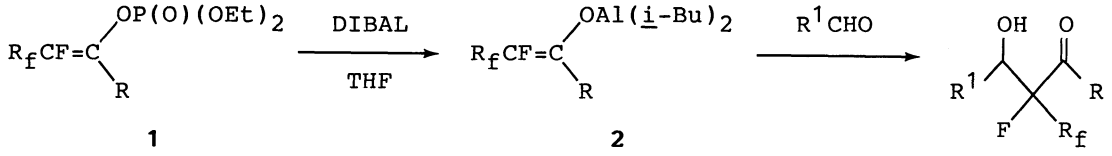
Takashi ISHIHARA,* Koichi YAMAGUCHI, and Manabu KUROBOSHI
Department of Industrial Chemistry, Faculty of Engineering,
Kyoto University, Yoshida, Sakyo-ku, Kyoto 606

1-Substituted F-1-alkenyl phosphates, prepared easily from F-alkyl ketones, were treated with diisobutylaluminium hydride in tetrahydrofuran at 0 °C for 5 min or at room temperature for 30 min to generate quantitatively the corresponding ketone aluminium(III) enolates, which underwent the aldol reaction with various aldehydes at 0 °C to give α-fluoro-α-F-alkyl β-hydroxy ketones in good to excellent yields.

Much attention has been focused on the chemistry of fluorinated ketone or ester enolates and their application to the synthesis of fluorine-containing analogs of natural compounds. Though recent reports indicate that monofluoro[1] and difluoro enolates[2] are very intriguing in organic synthesis,[3] the chemistry of enolates bearing an F-alkyl substituent on the carbon terminus in their zwitterionic structures is relatively little explored,[4] apparently due to the lack of suitable methods or precursors for generating these species.

We have recently reported that 1-substituted F-1-alkenyl phosphates (**1**), available from F-alkyl ketones and sodium diethyl phosphite,[5] can serve as a promising precursor for the enolate by use of the lithium aluminium hydride-copper(II) bromide combined reagent.[4b] However, this method suffers serious disadvantages such as a troublesome manipulation and variable yields of products.

Disclosed in this communication are a new highly efficient method for the generation of F-alkyl ketone aluminium(III) enolates (**2**) *via* the reductive dephosphorylation[6] of the phosphates **1** with diisobutylaluminium hydride and their aldol reactions with a variety of aldehydes giving the corresponding α-fluoro-α-F-alkyl β-hydroxy ketones (**3**) in good yields.



1 **2** **3**

To a solution of the phosphate **1** (1 mmol) in tetrahydrofuran (THF) (5 cm^3) was added dropwise diisobutylaluminium hydride (DIBAL) (1 mol dm^{-3} hexane solu-

Table 1. ^{19}F NMR Data for Enol Phosphates **1** and Enolates **2** ($R_f = CF_3$)

R		$\delta^{a)}$ for **1**	$\delta^{b)}$ for **2**
$CH_3(CH_2)_5$[c,d]	(E)	-65.9 (d, J=11.0, 3F)	-64.4 (d, J=13.4, 3F)
		-147.1 (m, 1F)	-171.0 (q, J=13.4, 1F)
	(Z)	-67.3 (d, J=9.8, 3F)	-66.3 (d, J=12.2, 3F)
		-160.2 (m, 1F)	-183.0 (m, 1F)
C_6H_5[d,e]	(E)	-65.6 (dd, J=11.6, 2.4, 3F)	-64.5 (d, J=14.7, 3F)
		-143.5 (dq, J=11.6, 6.1, 1F)	-167.5 (q, J=14.7, 1F)
	(Z)	-67.0 (dd, J=9.8, 2.4, 3F)	-66.4 (d, J=11.0, 3F)
		-156.6 (dq, J=9.8, 9.8, 1F)	-180.0 (q, J=11.0, 1F)

a) Expressed in ppm downfield from internal $CFCl_3$. b) Expressed in ppm downfield from external $CFCl_3$. c) E:Z = 73:27. d) The stereochemistry of **1** was tentatively determined by ^{19}F NMR. e) E:Z = 15:85.

tion, 5 mmol, 5 cm^3) at 0 °C under argon. This mixture was stirred at room temperature (25-27 °C) for 30 min (R = $CH_3(CH_2)_5$) or at 0 °C for 5 min (R = c-C_6H_{11} and C_6H_5). Acidic hydrolysis of the reaction mixture furnished the corresponding α-hydryl-F-alkyl ketone ($R_fCFHCOR$) quantitatively. When the reaction mixture was subjected to ^{19}F NMR analysis before hydrolysis, the intermediary enolates could be detected successfully and their half-lives were determined; 20 h and 1 h at room temperature for R = $CH_3(CH_2)_5$ and C_6H_5 ($R_f = CF_3CF_2$), respectively. The spectral data of the representative enolates are listed in Table 1, together with those of **1**. The phosphate **1** ($R_f = CF_3$, R = C_6H_5) has a long-range fluorine-phosphorus coupling (i.e., 2.4, 6.1, and 9.8 Hz) but the enolate does not. The ^{19}F NMR spectra of the enolates examined showed a marked resemblance to the spectra of **1**. These observations suggest a possible structure (**2**) for the in situ generated enolates, in which the diisobutylaluminium group is bound to the oxygen atom. The large vicinal fluorine-fluorine couplings (11-15 Hz) between a trifluoromethyl group and a vinylic fluorine are also suggestive of the structure **2**. Of most importance is that in all cases the isomer ratios of these enolates were identical with those of the starting phosphates. This fact indicates that the enolates are generated with retention of configuration of **1**; no interconversion occurs at all between their two geometrical isomers.

The reaction of these F-alkyl ketone aluminium(III) enolates **2** with carbonyl compounds was carried out. Thus, an aldehyde (3 mmol) was added dropwise at 0 °C to a solution which resulted from the above treatment of **1** (1 mmol) with DIBAL. After stirring for 15-30 min at the same temperature, the reaction mixture was hydrolyzed with dilute hydrochloric acid. Extraction with ether followed by drying, evaporation, and silica-gel column chromatography gave analytically pure β-hydroxy ketone **3**.[7] The results of the reaction are summarized in Table 2. Various aldehydes except 2,2-dimethylpropanal reacted smoothly with **2** to afford the corresponding β-hydroxy ketones **3** in high yields, whereas ketones such as cyclohexanone and acetophenone failed to react. A longer reaction time or a

Table 2. Aldol Reaction of Enolates 2 Generated from 1 with Aldehydes

Entry	Phosphate 1 R_f	R	E:Z[b]	Aldehyde	Yield/%[a] of 3	Isomer ratio[c]
1	CF_3	$CH_3(CH_2)_5$	73:27	CH_3CH_2CHO	77	67:33
2			73:27	$CH_3(CH_2)_2CHO$	83	62:38
3			73:27	$CH_3(CH_2)_5CHO$	81	59:41
4			73:27	(E)-CH_3CH=CHCHO	76	65:35
5			73:27	C_6H_5CHO	84	61:39
6	CF_3	C_6H_5	15:85	$CH_3(CH_2)_2CHO$	68[d]	46:54
7			12:88	C_6H_5CHO	78	39:61
8	CF_3CF_2	$CH_3(CH_2)_5$	65:35	CH_3CH_2CHO	76	71:29
9			72:28	$CH_3(CH_2)_2CHO$	71	68:32
10			65:35	$(CH_3)_2CHCHO$	59[e]	63:37
11			70:30	$CH_3(CH_2)_5CHO$	82	72:28
12			70:30	(E)-CH_3CH=CHCHO	73	68:32
13			70:30	C_6H_5CHO	70	51:49
14	CF_3CF_2	c-C_6H_{11}	35:65	$CH_3(CH_2)_2CHO$	80	45:55
15			35:65	(E)-CH_3CH=CHCHO	86	39:61
16			35:65	C_6H_5CHO	88	42:58
17	CF_3CF_2	C_6H_5	22:78	$CH_3(CH_2)_2CHO$	81	38:62
18			21:79	$(CH_3)_2CHCHO$	56[e]	22:78
19			21:79	(E)-CH_3CH=CHCHO	66	37:63
20			22:78	C_6H_5CHO	71	23:77

a) Isolated yields. b) Measured by ^{19}F NMR. See footnote (d) in Table 1. c) Determined by ^{19}F NMR prior to isolation. The values are indicated in a ratio of threo to erythro isomer.[8,9] d) Conducted at -30 °C for 15 min by using 5 mmol of aldehyde. e) An excess (5-6 mmol) of aldehyde was employed.

higher temperature substantially lowered the yield of the product, due to either the retro-aldol reaction of **3** or the decomposition of **2**.[11] It should be noted that the ratios of threo to erythro isomers[8,9] of **3** nearly reflect the ratios of E- to Z-isomers of the phosphates **1**, or the enolates **2**. This result strongly suggests that the aldol reaction of **2** with aldehydes proceeds preferentially via a cyclic six-membered transition state.

In summary, a highly efficient method for the generation of F-alkyl ketone aluminium(III) enolates has been evolved through the dephosphorylation reaction of F-1-alkenyl phosphates **1** with DIBAL. This method can serve as a general and effective means for synthesizing α-fluoro-α-F-alkyl β-hydroxy ketones **3**, which are very difficult to obtain by other methods.

References

1) J.T. Welch and K.W. Seper, Tetrahedron Lett., 25, 5247 (1984); J.T. Welch, K.W. Seper, S. Eswarakrishnan, and J.S. Samartino, J. Org. Chem., 49, 4720 (1984); J.T. Welch and J.S. Samartino, ibid., 50, 3663 (1985).

2) M. Yamana, T. Ishihara, and T. Ando, Tetrahedron Lett., 24, 507 (1983); T. Ishihara, T. Yamanaka, and T. Ando, Chem. Lett., 1984, 1165; E.A. Hallinan and J. Fried, Tetrahedron Lett., 25, 2301 (1984); T. Taguchi, O. Kitagawa, T. Morikawa, T. Nishiwaki, H. Uehara, H. Endo, and Y. Kobayashi, ibid., 27, 6103 (1986); M. Kuroboshi and T. Ishihara, ibid., 28, 6481 (1987); O. Kitagawa, T. Taguchi, and Y. Kobayashi, ibid., 29, 1803 (1988); R.W. Lang and B. Schaub, ibid., 29, 2943 (1988); H. Greuter, R.W. Lang, and A.J. Romann, ibid., 29, 3291 (1988); T. Taguchi, O. Kitagawa, Y. Suda, S. Ohkawa, A. Hashimoto, Y. Iitaka, and Y. Kobayashi, ibid., 29, 5291 (1988); D.J. Burton and J.C. Easdon, J. Fluorine Chem., 38, 125 (1988).

3) S. Brandange, O. Dahlman, and L. Morch, J. Am. Chem. Soc., 103, 4452 (1981); J. Fried, E.A. Hallinan, and M.J. Szwedo, Jr., ibid., 106, 3871 (1984); S. Thaisrivongs, D.T. Pals, W.M. Kati, S.R. Turner, L.M. Thomasco, W. Watt, J. Med. Chem., 29, 2080 (1986); L.W. Hertel, J.S. Kroin, J.W. Misner, and J.M. Tustin, J. Org. Chem., 53, 2406 (1988).

4) a) T. Yokozawa, T. Nakai, and N. Ishikawa, Tetrahedron Lett., 25, 3987, 3991 (1984); b) M. Kuroboshi, Y. Okada, T. Ishihara, and T. Ando, ibid., 28, 3501 (1987); c) T. Yokozawa, N. Ishikawa, and T. Nakai, Chem. Lett., 1987, 1971; d) C.-P. Qian and T. Nakai, Tetrahedron Lett., 29, 4119 (1988).

5) T. Ishihara, Y. Okada, M. Kuroboshi, T. Shinozaki, and T. Ando, Chem. Lett., 1988, 819.

6) The reaction of enol phosphates and related compounds with organolithium or Grignard reagents has been used for generating metal enolates. See: I.J. Borowitz, E.W.R. Casper, R.K. Crouch, and K.C. Yee, J. Org. Chem., 37, 3873 (1972). Interestingly, the reductive dephosphorylation of nonfluorinated phosphates with DIBAL did not occur under the present reaction conditions.

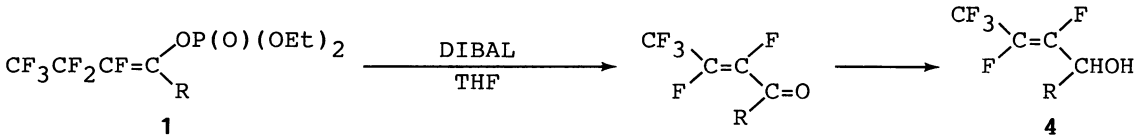
7) All isolated compounds exhibited satisfactory spectral and analytical data. Large-scale reactions were also performed to give good results.

8) The relative stereochemistry of **3** is given according to the nomenclature proposed by Noyori. See: R. Noyori, I. Ishida, and J. Sakata, J. Am. Chem. Soc., 105, 1598 (1983), footnote 32.

9) The configurational assignment of the threo (α-R_f–β-OH syn) and erythro (α-R_f–β-OH anti) isomers of **3** was made on the basis of stereochemical outcome in their stereoselective reduction[10] with organoaluminium hydride reagents.

10) Highly diastereoselective synthesis of 2-trifluoromethyl-1,3-diol systems is being studied. The detailed results will be reported in due course.

11) Treatment of **1** with DIBAL in refluxing THF produced the corresponding fluorinated (E)-allylic alcohols **4**[7] in good yields, as shown below.



1 **4**

R = $CH_3(CH_2)_5$ (73%); R = C_6H_5 (73%)
R = c-C_6H_{11} (72%); R = p-$CH_3OC_6H_4$ (60%)

(Received April 21, 1989)