Tetrahedron Letters,Vol.29,No.33,pp 4119-4122,1988	0040-4039/88 $3.00 + .00
Printed in Great Britain	Pergamon Press plc

PERFLUORO-ENOLATE CHEMISTRY:
FACILE GENERATION AND UNIQUE REACTIVITIES OF METAL F-1-PROPEN-2-OLATES

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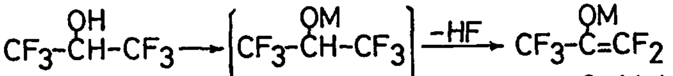
Summary: Extremely facile methods for generating the metal F-enolates $CF_3\text{-}C(OM)=CF_2$ (M=Li, Na, K) from $CF_3CH(OH)CF_3$ have been developed. Furthermore, the F-enolates are shown to exhibit a unique spectrum of reactivity including the aldol reactivity and the electrophilic reactivity toward organometallic reagents.

In view of the central position of enolate chemistry in synthetic organic chemistry, perfluorinated enolate (F-enolate) chemistry should, in principle, occupy an equally important position in organofluorine chemistry. Despite its great potential, however, F-enolate chemistry remains largely unexplored primarily because of the lack of general synthetic methods for suitable F-enolate precursors.[1,2] We now wish to report an extremely facile generation of metal F-propenolates 3 from the commercially available non-carbonyl precursor 1 and disclose its unique spectrum of reactivity toward electrophiles and nucleophiles.



$$CF_3\text{-}\overset{OH}{C}H\text{-}CF_3 \longrightarrow \left[CF_3\text{-}\overset{OM}{C}H\text{-}CF_3\right] \xrightarrow{-HF} CF_3\text{-}\overset{OM}{C}{=}CF_2$$

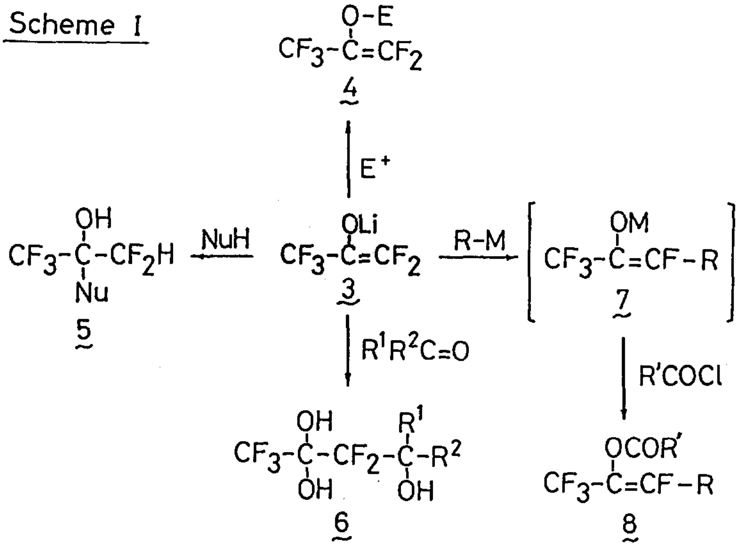
1　　2　　3 M=Li,Na,K

The generation method we have now developed is quite simple. Thus, alcohol 1 was treated with butyllithium (2 equiv.) in THF at -40°C for 4 h or, more conveniently, at 20°C for 20 min to generate F-enolate 3 (M=Li) in an essentially quantitative yield. Not unexpectedly, the lithium F-enolate is quite stable even at room temperature as probed by ^{19}F NMR spectroscopy.[3,4]

Generations of sodium (3, M=Na) and potassium F-enolate (3, M=K) are also feasible[5] by successive treatment of 1 with sodium hydride (1 eq) and butyllithium (1 eq) and with potassium hydride (1 eq) and butyllithium (1 eq), respectively, under similar conditions. Of interest is the observation that the ease of the dehydrofluorination of the alkoxides (2) significantly varied in the order: M=K>Na>Li.[6] This order is somewhat unexpected in view of the known order of ionic character of the M-O bonds, suggesting that the stronger coordination by F to $M^{\delta+}$ in 2 makes the elimination faster.[7] The role of the F→M coordination is evidenced by the independent finding that addition of 18-crown-6 considerably retarded the elimination of 2 (M=K).[8]

Next, we carried out reactions of the F-enolate thus generated with a wide variety of reagents. Our major concerns were whether F-enolate 3 still possesses the ambident nucleophilic reactivity like usual enolates and/or exhibits any unique reactivities that usual enolates do not. Scheme I and Table I show the wide spectrum of reactivity we have observed with 3 (M=Li).

Scheme I



The following features of the F-enolate reactivity are now revealed: (a) F-enolate 3 still shows the normal enolate reactivities, i.e., the O- and C-nucleophilicity, to afford various classes of polyfluorinated compounds (4 - 6) which are otherwise difficult to obtain. (b) In reactions with reagents bearing an active hydrogen, the initial protonation occurs at the β-carbon, not at the oxygen,[9] to yield the products of type 5. (c) F-enolate 3 is capable of undergoing the aldol reactions with various carbonyl partners to afford the adducts as their hydrate forms (6). Entry 13 is the first example of the crossed "perfluoro-aldol reaction." (d) More significantly, F-enolate 3 exhibits an electrophilic reactivity toward organometallc reagents to generate a geometric mixture of the β-alkylated F-enolates (7) via addition-elimination reaction. That means that 3 can act as a perfluoroolefin which is well known to undergo a similar type of reaction.[10]

Further noteworthy is the distinct effect of metal ion on reactivity of F-enolates 3. We found that both the aldol reactivity[11] and the electrophilic reactivity to alkyllithiums[12] remarkably varied in the order: M=K>Na>Li. While the order of aldol reactivity is just what one might predict, the order of electrophilicity is rather surprising. We suggest that the extent or strength of the $F \rightarrow M^{\delta+}$ might play a major role in governing the electrophilic reactivity.[7,13]

In summary, this work has opened the door to the hitherto unexplored F-enolate chemistry. We have now developed a very facile method for generating metal enolates 3 and demonstrated for the first time that such F-enolates exhibit the remarkably unique "triple reactivity", i.e., the O- and C-nucleophilicity and the C-electrophilicity. We are currently investigating the generality of the present methodology for generating F-enolates and also the chemistry of polyfluorinated enolates of type 7 described above.

Acknowledgment. This work was partially supported by the Grant-in-Aid for Scientific Research from the Japanese Government. We are grateful to Dr. M. Maruta for valuable disccussions and Central Glass Co. for kindly providing the starting alcohol.

Table I. Reactions of F-Enolate 3 (M=Li) with Various Reagents[a]

entry	reagent	product[b]	%yield[c]
1	PhCOCl	4a, E=COPh	82 (99)[d]
2	CF_3COCl	4b, E=$COCF_3$	72
3	Me_3SiCl	4c, E=$SiMe_3$	80
4	$(MeO)_2SO_2$	4d, E=Me	72[d]
5	H_2O	5a, Nu=OH	86
6	$PhCH_2OH$	5b, Nu=OCH_2Ph	71
7	$PhCONH_2$	5c, Nu=NHCOPh	74
8	$CHF(CO_2Et)_2$	5d, Nu=$CF(CO_2Et)_2$	61
9[e]	PhCHO	6'a[f]	72
10[e]	EtCHO	6b, R^1=Et, R^2=H	71
11[e]	PhCOMe	6c, R^1=Ph, R^2=Me	82
12[e]	cyclohexanone	6d, R^1, R^2= $-(CH_2)_5-$	93
13[e]	$(CF_3CF_2)_2CO$	6e, R^1, R^2=CF_2CF_3	74
14	n-BuLi	8a, R=n-Bu, R'=Me (72/28)[g]	71
15[h]	n-BuLi	8a (92/8)[g]	67[d]
16	PhLi	8b, R=Ph, R'=Me (77/23)[g]	64
17[i]	EtMgBr	8c, R=Et, R'=Ph (70/30)[g]	43
18[i]	PhMgBr	8b (83/17)[g]	48
19	vitride[j]	8e, R=H, R'=Ph	55

[a] Unless otherwise noted, all reactions were run in THF at room temperature for 2-5 h. [b] All the products were fully characterized by IR and ^1H- and ^{19}F-NMR spectra. [c] Refers to the isolated yield via distillation or column chromatography. [d] Determined by ^{19}F NMR assay. [e] Run at 0°C for 20-60 min. [f] The isolated product was not the hydrate form (6a), but the cyclized hemiacetal form, i.e., 2-trifluoromethyl-2-hydroxy-3,3-difluoro-4-phenyloxetane (6'a). [g] Refers to the E/Z ratio determined by ^{19}F NMR spectra. [h] Run at -78°C. [i] Carried out at 45°C for 24 h. [j] A commercial solution of $NaAlH_2(OCH_2CH_2OEt)_2$ in toluene.

References and Notes

1) For the multi-step preparations of CF_3COCF_2H and $CF_3C(OH)=CF_2$, see: "Syntheses of Fluoroorganic compounds"; Knunyants, I. L.; Yacobson, G. G., Eds.; Springer-verlag: Berlin, 1985; Part 2. For the recent efforts to prepare α-halo-*F*-ketone precursors, see: Jeong, I. H.; Burton, D. J.; Cox, D. G. *Tetrahedron Lett.* **1986**, *27*, 3709 and references therein.

2) There have been only a few reports on generation of *F*-enolates. (a) $CF_3C(OLi)=CF_2$ from CF_3-$C(OH)=CF_2$ and *n*-BuLi: Bekker, R. A.; Melikyan, G. G.; Dyatkin, B. L.; Knunyants, I. L. *Zh. Org. Khim.* **1976**, *12*, 1379 (no studies have been made on its chemistry). (b) $(CF_3)_2C=CF-O^-$ TAS^+ from $(CF_3)_2C=C=O$ and $(Me_2N)_3S^+(CH_3)_3SiF_2^-$: Farnham, W. B.; Middleton, W. J.; Fultz, W. C.; Smart, B. E. *J. Am. Chem. Soc.* **1986**, *108*, 3125.

3 The parent enol $CF_3C(OH)=CF_2$ is known to be remarkably stable and distillable without ketonization: Bekker, R. A.; Malikyan, G. G.; Dyatkin, B. L.; Knunyants, I. L. *Zh. Org. Khim.* **1975**, *11*, 1370. Also see: Hart, H.; Sasaoka, M. *J. Chem. Ed.* **1980**, *57*, 685. For the pioneering works of Knunyants' group on the chemistry of this *F*-enol, see: ref 2a and their earlier papers cited therein.

4) ^{19}F NMR (Et_2O, ex. CF_3CO_2H): δ -8.0 (d,d, J=9.4 and 22.6 Hz, CF_3), +30.3 (br. d, J=88.4 Hz, F *trans* to CF_3), and +41.3 (br. d, J=88.4, F *cis* to CF_3). The NMR data are fully consistent with the reported values in ref 2a.

5 The Na- and K-enolates show different ^{19}F NMR spectra from that of the Li-enolate. The δ_{CF_3}-values (Et_2O, ex. CF_3CO_2H), for instance, are -6.4 for M=Na and -7.0 for M=K. It should be noted that the K-enolate is relatively unstable and gradually decomposes at room temperature.

6) The *F*-enolate yields (after benzoylation) for the reactions run at -78 ° C for 4 h were 37% for M=Li, 81% for M=Na, and 91% for M=K.

7 This argument is based on the reasonable postulate that the more ionic the M-O bond, the greater extent of (or the stronger) the $F \rightarrow M^{\delta+}$ coordination.

8) The *F*-enolate yields (after benzoylation) for the reactions of **2** (M=K) with *n*-BuLi at -78°C for 4 h were 83% and only 19% in the absence and the presence of 18-crown-6 (1.0 eq), respectively.

9) The protonation at the oxygen should result in the formation of the parent enol.[3]

10) see, for example: Hudlicky, M. "Chemistry of Organic Fluorine Compounds", 2nd Ed.; Ellis Horwood: New York, 1976; Chapter 5.

11) The product yields for the aldol reactions with cyclohexanone at -25°C for 2.5 h were 18% for M=Li, 76% for M=Na, and 88% for M=K.

12) The yields of the β-alkylated *F*-enolate 7 (after acetylation) for the reactions with *n*-BuLi at -20°C for 2 h were 77% (*E*/*Z* = 84:16) for M=Li, 86% (*E*/*Z* = 79:21) for M=Na, and 100% (*E*/*Z* = 73:27) for M=K.

13) We are planning detailed structural studies and molecular orbital calculations on the *F*-enolates.

(Received in Japan 23 June 1988)