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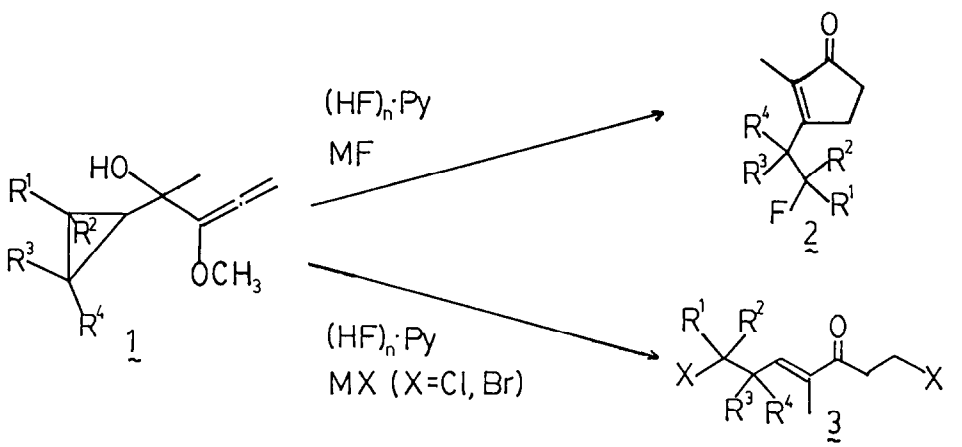
Synthesis of 3-Fluoroethylcyclopentenones via Rearrangement of Cyclopropyl Methoxyallenyl Carbinols Promoted by Hydrogen Fluoride-Pyridine-Metal Fluoride.

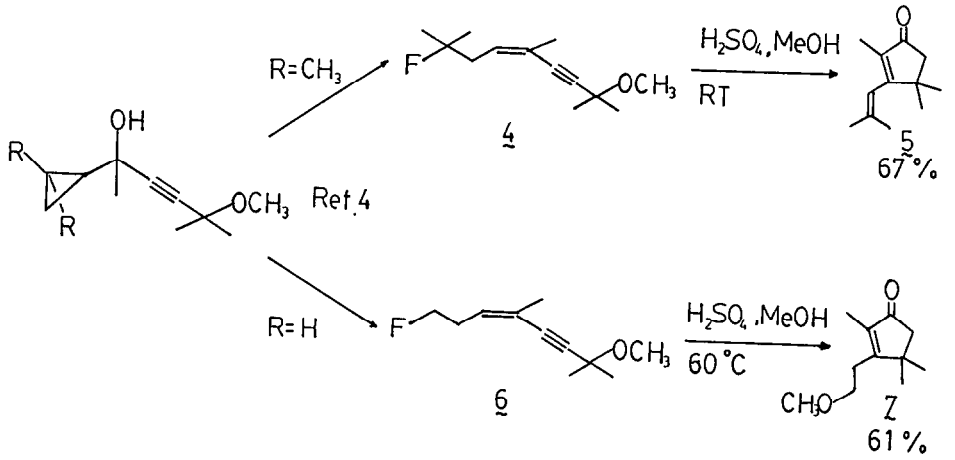
Makoto Shimizu* and Hirosuke Yoshioka*
The Institute of Physical and Chemical Research (RIKEN)
Wako, Saitama 351-01, Japan

Summary: 3-Fluoroethyl-2-cyclopenten-1-ones are prepared in a single step by treatment of cyclopropyl methoxyallenyl carbinols with $(HF)_n$.Py-metal fluoride.

2,3-Disubstituted cyclopentenones are essential cores for a number of important bioactive molecules of natural resources such as prostaglandin B, jasmonoids and pyrethrins.[1] Analogues monofluorinated at a specific position in the side chains of these molecules have become widely attempted in connection with the biorationalization works for new drug design.[2] However, many had encountered with difficulties in synthesizing the fluorinated cyclopentenoids either by annulation of fluorinated acyclics or by fluorination after annulation . We report a new single step synthesis of 3 fluoroethylcyclopentenones from cyclopropyl methoxyallenyl carbinols promoted by $(HF)_n$.Py-MF.



In principle, a Nazarov type cyclization is a convenient route to the substituted cyclopentenones from divinyl ketones or their equivalents.[3] Fluoro-enyns of type 4 and 6 prepared by the previously reported method[4] appeared to be applicable in the Nazarov cyclization. However, those compounds failed to cyclize to afford cyclopentenones under the typical fluorination conditions ($(HF)_n$.Py-$^i Pr_2NH$-NaF in CH_2Cl_2 at 0 °C),[4] and under a variety of more forcing conditions (H_2SO_4-MeOH, TfOH-MeOH, $(HF)_n$.Py-CH_2Cl_2, $(HF)_n$.Py-MeOH, $(HF)_n$.Py-NaF-MeOH, at rt--60 °C), giving fluorine-free dienone 5 and methoxyenone 7. The elimination of hydrogen fluoride may be owing to the strongly acidic conditions required for the conversion of the acetylene to a carbonyl functionality.



We then contemplated, as an intrinsic solution to the current problem, a one-step fluoro-annulation under milder conditions in which methoxyallene[5] was introduced as an essential precursor to the α, β-unsaturated carbonyl. The starting material **1** was readily prepared in good yield (>80%) by the addition of the lithiated methoxyallene to cyclopropyl ketones.[6] Treatment of the methoxyallenyl alcohol **1a** ($R^1=R^2=R^3=R^4=CH_3$) with $(HF)_n$.Py in dichloromethane at 0 °C in the presence of NaF gave **2a** in 50% yield. The results of fluoro-cyclopentenone annulation and the related reactions are shown in Table 1.

Choice of the solvent and the reaction temperature is very critical. In general, a better result was obtained when the reaction was carried out in CH_2Cl_2 or CH_2Cl_2-MeOH at 0 °C. The nature of metal fluoride speicies is also noteworthy: Among the fluorides examined (NaF, KHF_2, KF, CsF, SnF_2, NH_4F, n-Bu_4NF), NaF and KHF_2 gave better results, in which the metal fluorides appeared to increase the nucleophilicity[7] of a fluoride anion and to lower the acidity of hydrogen fluoride; the reaction became complex in the absence of metal fluorides and afforded **2** in low yield (<10%). These results indicate that a delicate control of the nucleophilicity and the acidity of poly-hydrogen fluoride by metal fluorides and solvents[8] is the key to the successful application of this modification to highly functionalized substrates. Furthermore, when the metal chloride or bromide is employed in place of the fluoride,[9] the non-annulated dihalogeno-enone **3** was a sole product (entries 9, 10 and 13).

Table 1. Reaction of 1 with $(HF)_n$.Py in the Presence of MX[a]

Entry	1	Additive	Product[b]	%yield[c]
1	1a ($R^1=R^2=R^3=R^4=Me$)	SnF_2	2a	23
2	1a	CsF	2a	39
3	1a	n-Bu_4NF[d]	2a	44

Table 1. Continued.

Entry	1	Additive	Product[b]	%yield[c]
4	1a	NH_4F	2a	45
5	1a	KF	2a	48
6	1a	KHF_2	2a	49
7	1a	NaF	2a	50
8	1a	NaF[e]	2a	58
9	1a	NaCl	3a (X=Cl)	52
10	1a	NH_4Br	3a (X=Br)	57
11	1b (R^1=R^2=Me, R^3=R^4=H)	NaF	2b	54
12	1c (R^1=Me, R^2=R^3=R^4=H)	NaF	2c	45
13	1c	NaCl	3c (X=Cl)	65
14	1d (R^1=R^2=R^3=R^4=H)	KHF_2	2d	32

[a]Reactions were carried out in CH_2Cl_2 at 0 °C for 2 hr. [b]All products gave satisfactory spectral data. [c]Isolated yield. [d]In chlorobenzene. [e]In CH_2Cl_2-MeOH.

The tetramethyl derivative 1a gave the best result (entry 8), whereas the yield of 2 decreased considerably with decreasing the number of substituents on the cyclopropane ring (entries 12 and 14). In the unsymmetrically substituted cases (entries 11 and 12), the cyclopropane ring opening proceeded to generate the most stable carbonium ion intermediate, giving preferentially the tertially or secondary fluorides.[10] In the acyclic dihalide (3) formation, the geometry of the resulting olefins was usually dominated in an *E*-configuration (>80:20).

As demonstrated above, control of the dual properties of poly-hydrogen fluoride as an acid and as a nucleophile by choosing a proper reaction medium (temp., solv., and metal fluoride) leads to a one-step synthesis of fluoroethylcyclopentenones which are hardly accessible even by multi-step pathways.

The following example represents a typical experimental procedure: To a solution of 1b (73 mg, 0.4 mmol) in dichloromethane(1 mL) in the presence of NaF (84 mg, 2.0 mmol) was added $(HF)_n$.Py (70% HF, 30% Py, 1 mL) at 0 °C . The mixture was stirred at 0 °C for 2 hr. An aq. solution of KF (2 mL) and ether (5 mL) were added, and the normal work-up gave an oil (58 mg), which was purified on preparative TLC (eluent: AcOEt/*n*-Hx = 1/4) to afford 2b (37 mg, 54%) as a colorless oil.

Acknowledgment. This work was supported by the grant in aid from the Ministry of Education, Science and Culture, Japan.

References and Notes

1. In addition to the popular bioactive cyclopentenoids mentioned in the text, the following natural products possess a particular skeleton of 2-methyl-2-cyclopenten-1-one: Taonianone: F. Kido, A. Abe, and A. Yoshikoshi, *J. Chem. Soc., Chem. Commun.*, 590 (1986); SO-A: F. Bohlmann and C. Zdero, *Phytochem.*, 17, 1669 (1978); Gnidididone: S. M. Kupchan, Y. Shizuri, R. L. Baxter, and H. R. Haynes, *J. Org. Chem.*, 42, 348 (1977); Violerythrin: S. Hertzberg and S. Liaaen-Jensen, *Acta Chem. Scand.*, 22, 1714 (1968); Cyperotundone: H. Hikino, K. Aota, and T. Takemoto, *Tetrahedron*, 23, 2169 (1967); Mexicanin D: W. Hertz, A. Romo de Vivor, and N. Viswanathan, *J. Am. Chem. Soc.*, 85, 19 (1963).
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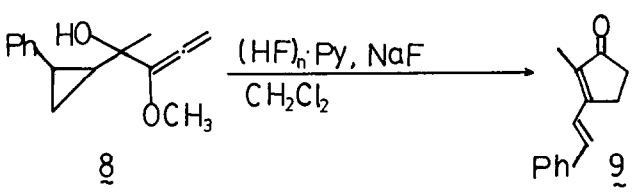
7. The monomeric fluoride ion is a strong nucleophile; see, G. A. Olah, J. T. Welch, Y. D. Vankar, M. Nojima, I. Kerekes, and J. A. Olah, *J. Org. Chem.*, 44, 3872 (1979).
8. Other solvents such as EtOH, DMF, CH_3CN, AcOEt, THF, Et_2O, and *n*-C_5H_{12} gave the desired product in poor yields, whereas PhCl, $CHCl_3$, and CCl_4 could be better employed.
9. It was reported that alcohols reacted with MX in $(HF)_n$.Py to give the corresponding alkyl halides, see ref. 7.
10. The phenyl substituted cyclopropane derivative **8** gave mainly the dienone **9**.



8 **9**

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