JOC*Note*

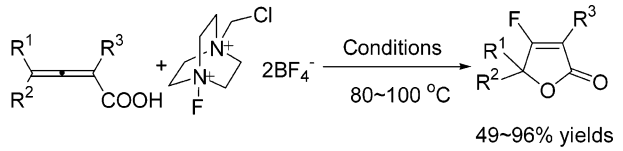
An Efficient Approach for Monofluorination via Aqueous Fluorolactonization Reaction of 2,3-Allenoic Acids with Selectfluor

Chao Zhou,[†] Zhichao Ma,[†] Zhenhua Gu,[‡] Chunling Fu,*[,†] and Shengming Ma*[,†,‡]

Laboratory of Molecular Recognition and Synthesis, Department of Chemistry, Zhejiang University, Hangzhou 310027, Zhejiang, P. R. China, and State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, P. R. China

masm@mail.sioc.ac.cn

Received November 8, 2007



Conditions A: MeCN, 10 equiv. H_2O or Conditions B: H_2O

We have developed a convenient method for the efficient monofluorination via the electrophilic fluorocyclization reaction of 2,3-allenoic acids with Selectfluor in MeCN in the presence of 10 equiv of H_2O or even in pure water to afford β-fluorobutenolides in moderate to high yields.

Although there are extremely rare organic fluorine metabolites in nature, bioactive organofluorine compounds play a very important role in modern medicinal chemistry;[1] therefore, it is not surprising that the development of new methods for the efficient introduction of fluorine atom into organic compounds is of current interest. Although fluorine itself is one of the most powerful reagents, it is usually too reactive for controllable and selective monofluorination reactions and definitely very dangerous.[1,2] On the other hand, protocols for the introduction of fluorine atom into organic molecules rely upon dozens of different reagents;[1,3] the most successful one is a new class of electrophilic fluorinating reagents with the general structure of R_2N-F or R_3N^+-F.[1,3,4] In this area, the development of the reagent Selectfluor **1** (1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate), also called F-TEDA-BF_4) represents a major advance for electrophilic fluorination since it is a reliable, mild, stable, inexpensive, yet effective reagent.[5] During our study on the chemistry of allenes,[6] we imagined that the fluorine chemistry of allenes, which has not been well established,[7] may be a nice way to introduce fluorine atoms into organic molecules. In this paper, we wish to disclose our recent observation on an effective monofluorination protocol via the electrophilic fluorolactonization of easily available 2,3-allenoic acids.[8]

In fact, we started our work by fluorinating a series of substituted unsaturated carboxylic acids, such as 3-undecaynoic acid or 4-phenyl-3-butenoic acid,[9] which afforded complicated mixtures (Scheme 1).

Further study indicates that although the fluorinating reaction of 2,3-allenoic acid **2a** with Selectfluor **1** in EtOH failed to afford β-fluorobutenolide **3a** (entry 1, Table 1), the reaction in EtOH/H_2O (20:1) afforded **3a** in 50% yield together with some byproducts (entry 2, Table 1), indicating the effect of H_2O. The reaction in DMF, DMA, or $MeNO_2$ in the presence of 10 equiv of H_2O afforded **3a** in 63−76% yields (entries 3−5, Table 1). Further screening led to the observation that MeCN is the best

* To whom correspondence should be addressed. Tel: 86-21-549-25147. Fax: 86-21-641-67510.
[†] Zhejiang University.
[‡] Chinese Academy of Sciences.

(1) Kirsch, P. *Modern Fluoroorganic Chemistry*, 1st ed.; Wiley-VCH: Weinheim, 2004.

(2) (a) Rozen, S. *Acc. Chem. Res.* **1996**, *29*, 243. (b) Rozen, S. *Acc. Chem. Res.* **1988**, *21*, 307.

(3) (a) Middleton, W. J. *J. Org. Chem.* **1975**, *40*, 574. (b) Barton, D. H. R.; Godinho, L. S.; Hesse, R. H.; Pechet, M. M. *Chem. Commun.* **1968**, 804. (c) Schack, C. J. K.; Christe, O. *Inorg. Chem.* **1979**, *18*, 2619. (d) Tius, M. A. *Tetrahedron* **1995**, *51*, 6605. (e) Schmutzler, R. *Angew. Chem., Int. Ed.* **1968**, *7*, 440. (f) Rozen, S. *Chem. Rev.* **1996**, *96*, 1717.

(4) (a) Umemoto, T.; Kawada, K.; Tomita, K. *Tetrahedron Lett.* **1986**, *27*, 4465. (b) Umemoto, T.; Fukami, S.; Tomizawa, G.; Harasawa, K.; Kawada, K.; Tomita, K. *J. Am. Chem. Soc.* **1990**, *112*, 8563. (c) Resnati, G.; DesMarteau, D. D. *J. Org. Chem.* **1991**, *56*, 4925. (d) DesMarteau, D. D.; Xu, Z.-Q.; Witz, M. *J. Org. Chem.* **1992**, *57*, 629.

(5) (a) Banks, R. E. (Air Products and Chemicals, Inc.) US 5,086,178, 1992, 9. (b) Banks, R. E.; Lawrence, N. J.; Popplewell, A. L. *Synlett* **1994**, 831. (c) Banks, R. E.; Besheesh, M. K.; Mohialdin-Khaffaf, S. N.; Sharif, I. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2069. (d) Nyffeler, P. T.; Duron, S. G.; Burkart, M. D.; Vincent, S. P.; Wong, C.-H. *Angew. Chem., Int. Ed.* **2005**, *44*, 192. (e) Singh, R. P.; Shreeve, J. M. *Acc. Chem. Res.* **2004**, *37*, 31.

(6) For reviews on the chemistry of allenes, see: (a) Zimmer, R.; Dinesh, C.; Nandanan, E.; Khan, F. *Chem. Rev.* **2000**, *100*, 3067. (b) Marshall, J. A. *Chem. Rev.* **2000**, *100*, 3163. (c) Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2000**, *39*, 3590. (d) Bates, R.; Satcharoen, V. *Chem. Soc. Rev.* **2002**, *31*, 12. (e) Sydnes, L. *Chem. Rev.* **2003**, *103*, 1133. (f) Ma, S. *Acc. Chem. Res.* **2003**, *36*, 701. (g) Brandsma, L.; Nedolya, N. A. *Synthesis* **2004**, 735. (h) Tius, M. A. *Acc. Chem. Res.* **2003**, *36*, 284. (i) Wei, L.-L.; Xiong, H.; Hsung, R. P. *Acc. Chem. Res.* **2003**, *36*, 773. (j) Lu, X.; Zhang, C.; Xu, Z. *Acc. Chem. Res.* **2001**, *34*, 535. (k) Wang, K. K. *Chem. Rev.* **1996**, *96*, 207. (l) Ma, S. *Chem. Rev.* **2005**, *105*, 2829. (m) Ma, S. *Aldrichim. Acta* **2007**, *40*, 91. For a monograph on the chemistry of allenes, see: Krause, N.; Hashmi, A. S. K. *Modern Allene Chemistry*; Wiley-VCH: Weinheim, 2004. For a recent review on the synthesis of allenes: Brummond, K. M.; DeForrest, J. E. *Synthesis* **2007**, 795.

(7) The reports on the fluorination based on allenes are very limited. For electrophilic monofluorination of 1,2- or 2,3-allenylsilanes, see: (a) Carroll, L.; Pacheco, M. C.; Garcia, L.; Gouverneur, V. *Chem. Commun.* **2006**, 4113. (b) Pacheco, M. C.; Gouverneur, V. *Org. Lett.* **2005**, *7*, 1267.

(8) For a most recent review on electrophilic cyclization of functionalized allenes, see: Krause, N.; Hashmi, A. S. K. *Modern Allene Chemistry*; Wiley-VCH: Weinheim, 2004; Chapter 10. For electrophilic halolactonization of 2,3-allenoic acids or 2,3-allenoates from this group, see: (a) Fu, C.; Ma, S. *Eur. J. Org. Chem.* **2005**, 2942. (b) Ma, S.; Shi, Z.; Yu, Z. *Tetrahedron Lett.* **1999**, *40*, 2393. (c) Ma, S.; Wu, B.; Shi, Z. *J. Org. Chem.* **2004**, *69*, 1429.

(9) (a) For fluorolactonization of 4-phenyl-3-butenoic acid with Selectfluor, see: Serguchev, Yu. A.; Lourie, L. F.; Shevchenko, G. V.; Chernega, A. N. *Zh. Org. ta Farm. Khim.* **2005**, *3*, 28. (b) For fluorolactonization of norbornenecarboxylic acids with Selectfluor and XeF_2, see: Lourie, L. F.; Serguchev, Y. A.; Shevchenko, G. V.; Ponomarenko, M. V.; Chernega, A. N.; Rusanov, E. B.; Howard, J. A. K. *J. Fluorine Chem.* **2006**, *127*, 377. (c) For fluorolactonization of 4-alkenoic acid derivatives with *N*-fluoropentachloropyridinium triflate, see: Okada, M.; Nakamura, Y.; Horikawa, H.; Inoue, T.; Taguchi, T. *J. Fluorine Chem.* **1997**, *82*, 157. In most cases shown above, the reaction afforded a mixture of fluorine-containing lactones with poor selectivity.

10.1021/jo702409y CCC: $40.75
Published on Web 12/23/2007

SCHEME 1. Fluorinating of Substituted Unsaturated Carboxylic Acids

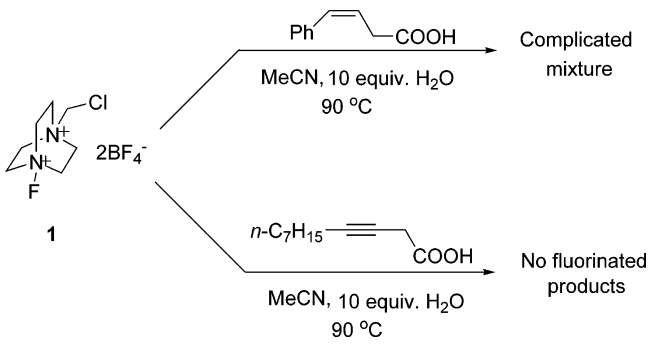
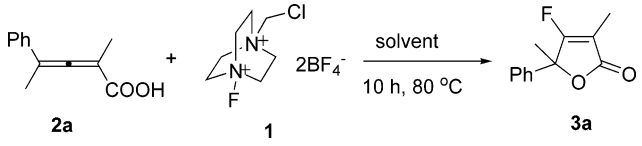


TABLE 1. Selectfluor-Mediated Lactonization Reaction of 2,4-Dimethyl-4-phenyl- 2,3-butadienoic Acid 2a



entry	solvent	H_2O (equiv)	**1** (equiv)	yield of **3a**[a] (%)
1	EtOH		2.0	no reaction
2[b]	EtOH/H_2O = 20:1		2.0	50
3	DMA	10	2.0	63
4	CH_3NO_2	10	2.0	69
5	DMF	10	2.0	76
6	CH_3CN	10	2.0	85
7	CH_3CN		2.0	71
8	CH_3CN	10	1.1	86
9[c]	H_2O		1.1	78

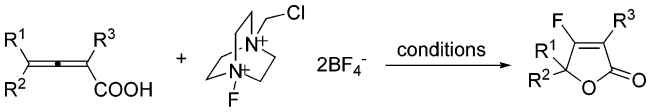
[a] NMR yield. [b] Byproducts were also formed. [c] The reaction was conducted at 90 °C.

solvent (compare entry 6 with entry 8 in Table 1; the reaction conditions of entry 8 are defined as conditions A). The reaction in MeCN in the absence of H_2O afforded **3a** in a relatively lower yield (entry 7, Table 1). Furthermore, the reaction may also be performed in pure water with just 1.1 equiv of Selectfluor **1** (entry 9, Table 1, defined as conditions B).

With the optimized reaction conditions A and B in hand, the reaction of Selectfluor **1** with phenyl- and alkyl-substituted 2,3-allenoic acids **2** producing the corresponding β-fluorobutenolide derivatives was studied. It was observed that with at least one phenyl group at the 4-position of the 2,3-allenoic acid, the reaction of the fully substituted (entries 1−7, Table 2) and 4,4-disubstituted (entries 8−10, Table 2) 2,3-allenoic acids afforded the β-fluorobutenolides in good yields under conditions A and/or B. With 2-alkyl-4-phenyl-2,3-allenoic acids **2h** and **2i**, when conditions A or B were applied, the reaction at 90 °C was slow and low-yielding (entries 11, 12, and 14, Table 2); thus, the reaction of **2h** and **2i** in MeCN in the presence of 10 equiv of H_2O was conducted at 95−100 °C in a reaction tube with a screw cap to afford the corresponding products **3h** and **3i** in 49% and 64% yields, respectively (entries 13 and 15, Table 2). Conditions A are also applicable to fully alkyl-substituted substrate **2j** (compare entry 16 with entry 17, Table 2).

In conclusion, we have developed a convenient method for the efficient monofluorination via the electrophilic fluorocyclization reaction of 2,3-allenoic acids with Selectfluor **1** in MeCN in the presence of 10 equiv of H_2O or even in pure water. Although the effect of water is not clear yet, we reasoned that

TABLE 2. Selectfluor-Mediated Lactonization Reactions of Different Substituted 2,3-Allenoic Acids



entry	R^1	R^2	R^3	conditions	isolated yield of **3** (%)
1	Ph	Me	Me (**2a**)	A	81 (**3a**)
2	Ph	Me	Me (**2a**)	B	75 (**3a**)
3	Ph	Et	*n*-Pr (**2b**)	A	81 (**3b**)
4	Ph	Et	*n*-Pr (**2b**)	B	59 (**3b**)
5	Ph	Et	Me (**2c**)	B	86 (**3c**)
6	Ph	Ph	Me (**2d**)	A	96 (**3d**)
7	Ph	Ph	*n*-Pr (**2e**)	A	94 (**3e**)
8	Ph	Me	H (**2f**)	A	61 (**3f**)
9	Ph	Me	H (**2f**)	B	70 (**3f**)
10	Ph	Ph	H (**2g**)	A	65 (**3g**)
11	Ph	H	*n*-Pr (**2h**)	A[a]	39 (**3h**)
12	Ph	H	*n*-Pr (**2h**)	B	9[b] (**3h**)
13	Ph	H	*n*-Pr (**2h**)	A[a,c]	49 (**3h**)
14	Ph	H	Me (**2i**)	B	19 (**3i**)
15	Ph	H	Me (**2i**)	A[a,d]	64 (**3i**)
16	$(CH_2)_4$		Me (**2j**)	A	53 (**3j**)
17	$(CH_2)_4$		Me (**2j**)	B[e]	34 (**3j**)

[a] 1.5 equiv of Selectfluor **1** was used. [b] NMR yield; 52% of **2h** was recovered. [c] The reaction was conducted at 100 °C in a reaction tube with a screw cap for 18 h. [d] The reaction was conducted at 95 °C in a reaction tube with a screw cap. [e] 1.2 equiv of Selectfluor **1** was used.

the hydrogen bonding between Selectfluor and H_2O may facilitate the electrophilic fluorocyclization. Due to the easily availability of 2,3-allenoic acids[10] and Selectfluor as well as the importance of butenolides[11−14] and monofluorides,[1,5] this reaction may be useful in organic synthesis and medicinal chemistry. Further studies in this area are being conducted in our laboratory.

Experimental Section

Synthesis of 4-Fluoro-3,5-dimethyl-5-phenyl-2(5*H*)-furanone (3a). Typical procedure for conditions A: To a solution of **2a** (94.0 mg, 0.5 mmol) in 5.0 mL of MeCN was added subsequently 90 μL (10 equiv) of H_2O and 194.5 mg (0.55 mmol) of Selectfluor **1**. After the reaction mixture was stirred at 80 °C for 10 h as monitored by TLC, it was quenched with 10 mL of water, extracted with diethyl ether (30 + 25 × 2 mL), washed with brine, and dried over anhydrous Na_2SO_4. Evaporation and column chromatography

(10) (a) Ma, S.; Wu, S. *J. Org. Chem.* **1999**, *64*, 9314. (b) Clinet, J. C.; Linstrumelle, G. *Synthesis* **1981**, 875. (c) Marshall, J. A.; Wolf, M. A.; Wallace, E. M. *J. Org. Chem.* **1997**, *62*, 367.

(11) For reviews on the synthesis of butenolides, see: (a) Negishi, E.; Kotora, M. *Tetrahedron* **1997**, *53*, 6707. (b) Rao, Y. S. *Chem. Rev.* **1976**, *76*, 625. (c) Knight, D. W. *Contemp. Org. Synth.* **1994**, *1*, 287. (d) Bruckner, R. *Curr. Org. Chem.* **2001**, *5*, 679. (e) Carter, N. B.; Nadany, A. E.; Sweeney, J. B. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2324.

(12) For some of the most recent examples, see: (a) Marshall, J. A.; Piettre, A.; Paige, M. A.; Valeriote, F. *J. Org. Chem.* **2003**, *68*, 1780. (b) Brown, S. P.; Goodwin, N. C.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 1192. (c) Linclau, B.; Boydell, A. J.; Clarke, P. J.; Horan, R.; Jaequet, C. *J. Org. Chem.* **2003**, *68*, 1821. (d) Patil, S. N.; Liu, F. *Org. Lett*, **2007**, *9*, 195. (e) Adrio, J.; Carretero, J. C. *J. Am. Chem. Soc.* **2007**, *129*, 778. (f) Maulide, N.; Marko, I. E. *Org. Lett.* **2006**, *8*, 3705. (g) Ma, S.; Lu, L.; Lu, P. *J. Org. Chem.* **2005**, *70*, 1063. (h) Kong, K.; Romo, D. *Org. Lett.* **2006**, *8*, 2909. (i) Marshall, J. A.; Sabatini, J. J. *Org. Lett.* **2006**, *8*, 3557.

(13) For reviews on biological importance of butenolide derivatives, see: (a) Rassu, G.; Zanardi, F.; Battistini, L.; Casiraghi, G. *Synlett* **1999**, 1333. (b) Casiraghi, G.; Zanardi, F.; Appendino, G.; Rassu, G. *Chem. Rev.* **2000**, *100*, 1929. (c) Casiraghi, G.; Zanardi, F.; Rassu, G. *Pure Appl. Chem.* **2000**, *72*, 1645. (d) Bur, S. K.; Martin, S. F. *Tetrahedron* **2001**, *57*, 3221. (e) Martin, S. F. *Acc. Chem. Res.* **2002**, *35*, 895.

on silica gel (petroleum ether/ethyl acetate = 20:1) afforded **3a** (83.1 mg, 81%): oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46−7.41 (m, 2H), 7.40−7.32 (m, 3H), 1.89 (s, 3H), 1.80 (d, J = 2.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.5 (d, J = 297.6 Hz), 170.7 (d, J = 21.8 Hz), 137.2 (d, J = 3.2 Hz), 128.76, 128.73, 124.7, 103.1 (d, J = 7.6 Hz), 82.2 (d, J = 20.5 Hz), 24.0 (d, J = 3.1 Hz), 5.8 (d, J = 2.7 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ −111.6; IR (neat) ν (cm^{-1}) 1775, 1727, 1496, 1448, 1336, 1080, 1048; MS (70 eV, EI) m/z 206 (M^+, 7.48), 163 (100); HRMS calcd for $C_{12}H_{11}O_2F$ (M^+) 206.0743, found 206.0753.

Typical procedure for conditions B: To a solution of **2a** (56.5 mg, 0.3 mmol) in 3.0 mL of H_2O was added with stirring 116.8 mg (0.33 mmol) of Selectfluor **1**. After the reaction mixture was stirred at 90 °C for 10 h as monitored by TLC, it was extracted with diethyl ether (30 + 25 × 2 mL), washed with brine, and dried over anhydrous Na_2SO_4. Evaporation and column chromatography on silica gel (petroleum ether/ethyl acetate = 20:1) afforded **3a** (46.3 mg, 75%).

Acknowledgment. Financial support from the National Natural Science Foundation of China (20572093), Major State Basic Research and Development Program (2006CB8061007), and the Cheung Kong Scholar Program is greatly appreciated. This work was conducted at Zhejiang University. We thank Zhao Fang in our group for reproducing the results presented in entries 2, 4, and 16 of Table 2.

Supporting Information Available: Experimental procedures and copies of ^{1}H and ^{13}C NMR spectra of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO702409Y