

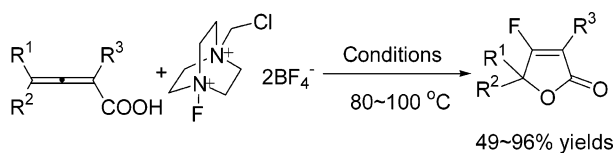
## An Efficient Approach for Monofluorination via Aqueous Fluorolactonization Reaction of 2,3-Allenic Acids with Selectfluor

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Conditions A: MeCN, 10 equiv. H<sub>2</sub>O or Conditions B: H<sub>2</sub>O

We have developed a convenient method for the efficient monofluorination via the electrophilic fluorocyclization reaction of 2,3-allenic acids with Selectfluor in MeCN in the presence of 10 equiv of H<sub>2</sub>O or even in pure water to afford  $\beta$ -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;<sup>1</sup> 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.<sup>1,2</sup> On the other hand, protocols for the introduction of fluorine atom into organic molecules rely upon dozens of different reagents;<sup>1,3</sup> the most successful one is a new class of electrophilic fluorinating reagents with the general structure of R<sub>2</sub>N-F or R<sub>3</sub>N<sup>+</sup>-F.<sup>1,3,4</sup> In this area, the development of the reagent Selectfluor **1** (1-chloromethyl-4-fluoro-1,4-diazonia-bicyclo[2.2.2]octane bis(tetrafluoroborate), also called F-TEDA-

BF<sub>4</sub>) represents a major advance for electrophilic fluorination since it is a reliable, mild, stable, inexpensive, yet effective reagent.<sup>5</sup> During our study on the chemistry of allenes,<sup>6</sup> we imagined that the fluorine chemistry of allenes, which has not been well established,<sup>7</sup> 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-allenic acids.<sup>8</sup>

In fact, we started our work by fluorinating a series of substituted unsaturated carboxylic acids, such as 3-undecyenoic acid or 4-phenyl-3-butenic acid,<sup>9</sup> which afforded complicated mixtures (Scheme 1).

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

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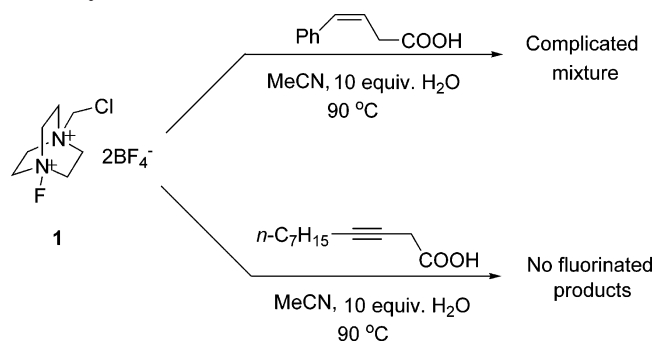
<sup>‡</sup> Chinese Academy of Sciences.

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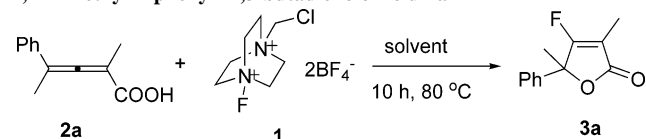
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### SCHEME 1. Fluorinating of Substituted Unsaturated Carboxylic Acids



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



entry	solvent	H <sub>2</sub> O (equiv)	1 (equiv)	yield of 3a <sup>a</sup> (%)
1	EtOH		2.0	no reaction
2 <sup>b</sup>	EtOH/H <sub>2</sub> O = 20:1		2.0	50
3	DMA	10	2.0	63
4	CH <sub>3</sub> NO <sub>2</sub>	10	2.0	69
5	DMF	10	2.0	76
6	CH <sub>3</sub> CN	10	2.0	85
7	CH <sub>3</sub> CN		2.0	71
8	CH <sub>3</sub> CN	10	1.1	86
9 <sup>c</sup>	H <sub>2</sub> O		1.1	78

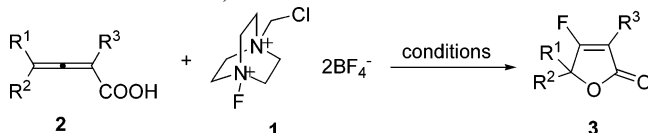
<sup>a</sup> NMR yield. <sup>b</sup> Byproducts were also formed. <sup>c</sup> The reaction was conducted at 90 °C.

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<sub>2</sub>O 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  $\beta$ -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  $\beta$ -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<sub>2</sub>O 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<sub>2</sub>O 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 <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	conditions	isolated yield of <b>3</b> (%)
1	Ph	Me	Me ( <b>2a</b> )	A	81 ( <b>3a</b> )
2	Ph	Me	Me ( <b>2a</b> )	B	75 ( <b>3a</b> )
3	Ph	Et	<i>n</i> -Pr ( <b>2b</b> )	A	81 ( <b>3b</b> )
4	Ph	Et	<i>n</i> -Pr ( <b>2b</b> )	B	59 ( <b>3b</b> )
5	Ph	Et	Me ( <b>2c</b> )	B	86 ( <b>3c</b> )
6	Ph	Ph	Me ( <b>2d</b> )	A	96 ( <b>3d</b> )
7	Ph	Ph	<i>n</i> -Pr ( <b>2e</b> )	A	94 ( <b>3e</b> )
8	Ph	Me	H ( <b>2f</b> )	A	61 ( <b>3f</b> )
9	Ph	Me	H ( <b>2f</b> )	B	70 ( <b>3f</b> )
10	Ph	Ph	H ( <b>2g</b> )	A	65 ( <b>3g</b> )
11	Ph	H	<i>n</i> -Pr ( <b>2h</b> )	A <sup>a</sup>	39 ( <b>3h</b> )
12	Ph	H	<i>n</i> -Pr ( <b>2h</b> )	B	9 <sup>b</sup> ( <b>3h</b> )
13	Ph	H	<i>n</i> -Pr ( <b>2h</b> )	A <sup>a,c</sup>	49 ( <b>3h</b> )
14	Ph	H	Me ( <b>2i</b> )	B	19 ( <b>3i</b> )
15	Ph	H	Me ( <b>2i</b> )	A <sup>a,d</sup>	64 ( <b>3i</b> )
16	(CH <sub>2</sub> ) <sub>4</sub>		Me ( <b>2j</b> )	A	53 ( <b>3j</b> )
17	(CH <sub>2</sub> ) <sub>4</sub>		Me ( <b>2j</b> )	B <sup>e</sup>	34 ( <b>3j</b> )

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

the hydrogen bonding between Selectfluor and H<sub>2</sub>O may facilitate the electrophilic fluorocyclization. Due to the easily availability of 2,3-allenoic acids<sup>10</sup> and Selectfluor as well as the importance of butenolides<sup>11–14</sup> and monofluorides,<sup>1,5</sup> 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(5H)-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  $\mu$ L (10 equiv) of H<sub>2</sub>O 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  $\times$  2 mL), washed with brine, and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. Evaporation and column chromatography

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on silica gel (petroleum ether/ethyl acetate = 20:1) afforded **3a** (83.1 mg, 81%): oil;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.46–7.41 (m, 2H), 7.40–7.32 (m, 3H), 1.89 (s, 3H), 1.80 (d,  $J = 2.4$  Hz, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  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);  $^{19}\text{F}$  NMR (282 MHz,  $\text{CDCl}_3$ )  $\delta$  –111.6; IR (neat)  $\nu$  ( $\text{cm}^{-1}$ ) 1775, 1727, 1496, 1448, 1336, 1080, 1048; MS (70 eV, EI)  $m/z$  206 ( $\text{M}^+$ , 7.48), 163 (100); HRMS calcd for  $\text{C}_{12}\text{H}_{11}\text{O}_2\text{F}$  ( $\text{M}^+$ ) 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  $\text{H}_2\text{O}$  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  $\times$  2 mL), washed with brine, and dried over anhydrous  $\text{Na}_2\text{SO}_4$ . Evaporation and column chromatography

on silica gel (petroleum ether/ethyl acetate = 20:1) afforded **3a** (46.3 mg, 75%).

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

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