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# Acid-catalyzed conjugate additions to 3-fluorobutenone

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ABSTRACT

3-Fluorobutenone (**2**) reacts under Zn(II) catalysis in ethanol solution with active methylene compounds such as anthrone and aromatic phenols to give products of the addition of one unit of 3-fluorobutenone.

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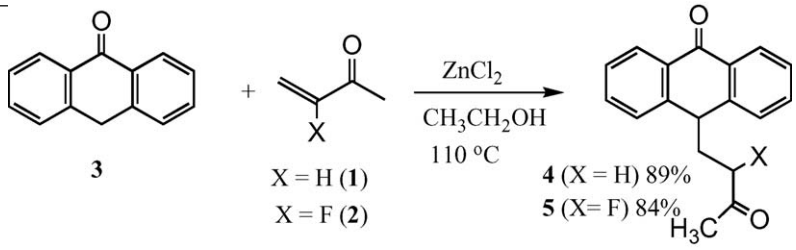
## 1. Introduction

Methyl vinyl ketone (MVK, **1**) is widely known for its versatility in organic reactions serving as a Michael acceptor [1,2], a Diels-Alder dienophile [2–4] and as a polymerization monomer [5]. 3-Fluorobutenone (**2**), a fluorinated analog of MVK, is known but has received only limited attention in the synthesis of fluorinated materials. Wakselman and co-worker [6] used **2** in the Robinson annulation procedure with cyclohexanone, and Schlosser et al. used **2** in addition reactions at both the carbonyl function and the alkene function [7,8]. Haufe has used α-fluorenones in the Diels-Alder reaction [9]. We have demonstrated the utility of **2** in the Heck reaction [10]. In this paper we describe the acid-catalyzed addition of **2** with several substrates that can display enolic forms.

## 2. Results and discussion

Anthrone (**3**) undergoes acid-catalyzed conjugate addition with **1** to give a mono addition adduct whereas under base-catalyzed reaction it gives a bis-Michael product [1,2]. When we used 3-fluorobutenone (**2**) in the reaction with anthrone under zinc(II) catalysis we observed only the mono-Michael adduct. Under base catalysis the reaction between **2** and anthrone gave a very complex mixture. Because of the mono addition selectivity observed with the zinc(II)-catalyzed reaction we studied several other substrates to enhance the reaction scope.




The substrates shown in Table 1 gave moderate to good yields of mono-Michael adduct. Only diethyl malonate and acetophenone showed conjugate addition products *alpha* to the carbonyl group. Several other 1,3-diketones failed to react at all with **2**. These substrates consisted of pentane-2, 4-dione, 3-methylpentan-2, 4-dione, 2-acetylcyclohenanone and 4,4-dimethylcyclohexan-1, 3-dione.

The 1,4 adduct from 2-naphthol underwent internal cyclization and reaction with the solvent ethanol to give the benzochromene structure **17** shown in Scheme 1 below. Phenol is already known to react with **2** with sulfuric acid catalyst to give **11**, the compound responsible for raspberry odor [6]. Compound 15 also gave an odor of raspberry but none of the other products displayed and distinctive smells. In competitive reactions of 3-fluorobutenone (**2**) with butanone (**1**) in excess with 3,5-dimethylphenol (**12**) as

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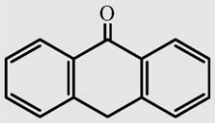
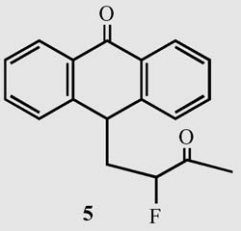
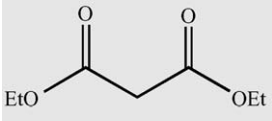
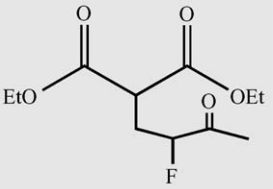
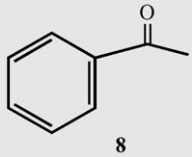
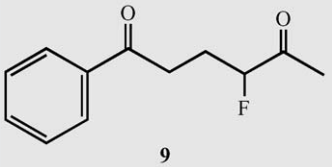
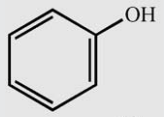
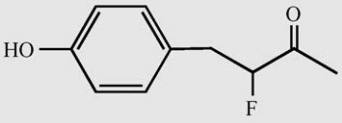
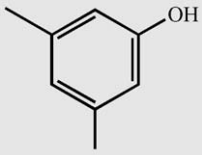
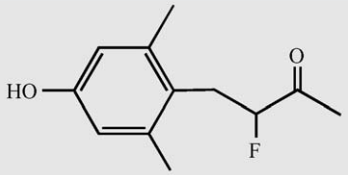
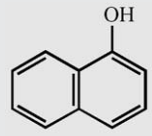
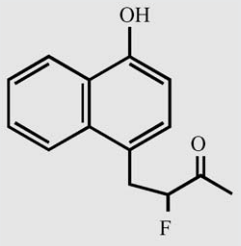
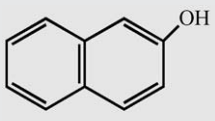
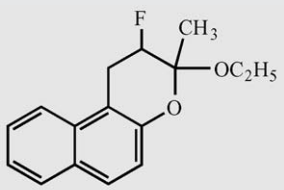
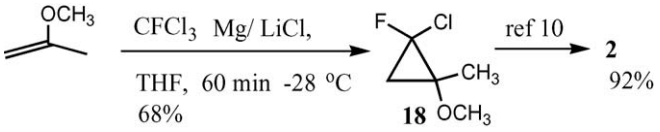
**Table 1**
Zinc chloride induced conjugate addition reactions.

| Substrate | Product | Yield (%) | F NMR ($CFCl_3$) |
|---|---|---|---|
|  **3** |  **5** | 84 | −189.9 (m) |
|  **6** |  **7** | 53 | −194.9 (m) |
|  **8** |  **9** | 52 | −194.6 (m) |
|  **10** |  **11** | 54 | −189.2 (m) |
|  **12** |  **13** | 84 | −188.9 (m) |
|  **14** |  **15** | 74 | −186.7 (m) |
|  **16** |  **17** | 43 | −193.0 (m) |

substrate we found equal reactivity between **1** and **2**. The results show that 3-fluorobutenone (**2**) is effective in the acid-catalyzed Michael reaction and that its reactivity is little influenced by the fluorine atom in comparison with **1**.

An alternate preparation of **2** comes from the aqueous ring opening of 1-chloro-2-methoxy-2-methylcyclopropane (**18**) in quinoline solution [10], a modified method described by Schlosser and co-workers [8]. The preparation of the cyclopropane from 2-methoxypropene and fluorodichloromethane described by Schlosser works well but the required fluorodichloromethane is now very expensive. We found that we could prepare **18** by addition of trichlorofluoromethane to 2-methoxypropane by using Mg/LiCl as described by Hu and Tu [11]. Trichlorofluoromethane is still readily available and has not suffered a substantial rise in cost.




## 3. Experimental procedure

### 3.1. General

$^1$H NMR data were recorded at 300.0 MHz with tetramethylsilane ($\delta$ = 0.00 ppm) as internal reference. $^{13}$C NMR spectra were recorded at 75.5 MHz with deuterated chloroform ($CDCl_3$ $\delta$ = 77.0 ppm) as internal reference. $^{19}$F NMR (Table 1) was recorded at 282.3 MHz with trifluoroacetic acid (TFA $\delta$ = 0.00 ppm) as external reference, and is corrected to $CFCl_3$. Deuterated chloroform was the solvent in all cases.

### 3.2. Preparation of 1-chloro-1-fluoro-2-methoxy-2-methylcyclopropane (18)

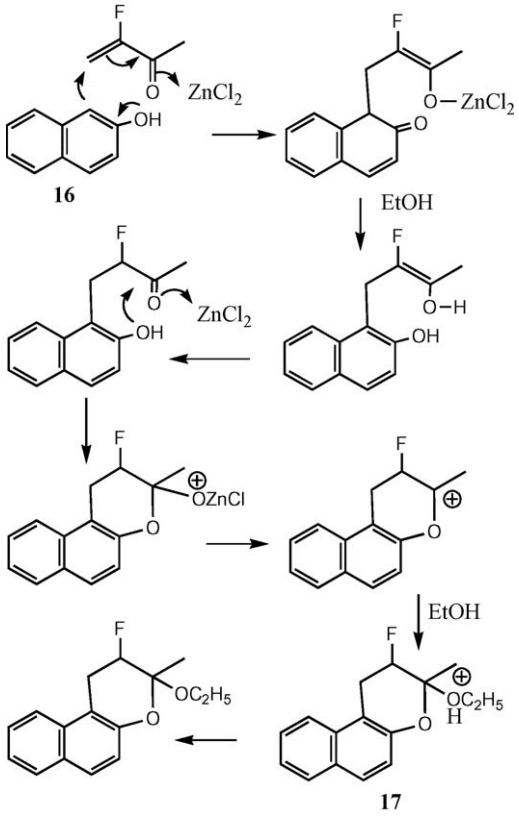
A 200 mL three-necked round bottom flask was flame dried. The necks were stoppered and argon gas was introduced into the flask. 1.34 g (55 mmol) magnesium and 2.12 g (50 mmol) LiCl were placed in the flask. Dry THF (40 mL) and 9.9 mL (7.23 g, 100 mmol)) 2-methoxypropene were charged by syringe. After cooling the flask to −23 °C (carbon tetrachloride/dry ice), 0.9 mL (1.37 g, 10 mmol) of trichlorofluoromethane was added drop wise by syringe. The reaction mixture was left 5 min and a second fraction of 4.6 mL (6.86 g, 50 mmol) of trichlorofluoromethane was added drop wise. The reaction mixture was stirred for 1 h and 5 mL water was added to quench the reaction. The product was extracted three times with 15 mL of diethyl ether. The organic phase was dried over $MgSO_4$ and the solvent was removed by fractional distillation to give

1-Chloro-1-fluoro-2-methoxy-2-methylcyclopropane **(18)**. (5.54 g, 40 mmol, 67% yield). $^1$H NMR $\delta$ 1.01–1.40 (m, $CH_2$, 2H) $\delta$ 1.50 (d, $J$ = 2 Hz, $CH_3$,3H), $\underline{\delta}$ 3.38 (s, $OCH_3$, 3H); $^{13}$C NMR $\delta$ 14.1–16.7 (d,$CH_3$), $\delta$ 27.9 (d, $CH_2$), $\delta$ 55.2 (d, $OCH_3$), $\delta$ 63.2 (d, C), $\delta$ 93.6–98.0 (d, CClF); $^{19}$F NMR (TFA = 0, 76.6 relative to $CDCl_3$) $\delta$ −141.6 (M, CF), $\delta$ −151.7 (m, CF) [8].

### 3.3. The preparation of 3-fluorobuteone (2) has been described previously. [10]

#### 3.3.1. General reaction procedure described for the preparation of 10-(2-fluoro-3-oxo-butyl)-4a,10-dihydro-9aH-anthracen-9-one (5)

A Fisher pressure hydrolysis tube was charged with 1.5 mL of ethanol, 350 mg (3.98 mmol) of 3-fluorobutenone **(2)**, 390 mg (2.01 mmol) of anthrone **(3)** and 18 mg of zinc chloride. The reaction mixture was heated for 3 h at 110 °C in a silicon oil bath.




**Scheme 1.**

The reaction mixture was filtered to remove unreacted anthrone. Eight fractions were collected in column chromatography with hexane/ethyl acetate gradient solvent system to purify the crude product. NMR showed 10-(2-fluoro-3-oxo-butyl)-4a, 10-dihydro-9aH-anthracen-9-one **(5)** in the fifth fraction (84 % yield). mp 164–167 °C, $^1$H NMR ($CDCL_3$, TMS) $\delta$ 2.13 (d, $J$ = 5 Hz, $CH_3$, 3H), 2.3 (m, $CH_2$ 2H), 4.5 (m, $J_{HF}$ = 50 Hz, CHF, 1H), 4.45 (m, CH, 1H), $\delta$ 7.4–8.4 (m, aromatic, 8H); $^{13}$C NMR ($CDCl_3$, TMS) $\delta$ 26.1 (d, $J$ = 5 Hz, $CH_3$), 39.0 (d, $J$ = 21 Hz, $CH_2$), 43.9 (CH), $\delta$ 93.2 (d, $J$ = 187 Hz, CHF), 127.0, 128.2, 133.1, 134.0, 142.8 144.0 (aromatic), 184.5 (s, CO), 207.0 (d, $J$ = 26 Hz, CO).

### 3.4. Analytical data for the Michael addition products in Table 1

(All compounds gave satisfactory C, H, and F elemental analysis data).

2-(2-Fluoro-3-oxo-butyl)-malonic acid diethyl ester **(7):** $^1$H NMR ($CDCL_3$, TMS) $\delta$ 1.15 (t, $J$ = 7 Hz, $CH_3$, 6H), 2.1 (s, $CH_3$, 3H), 2.23 (d, $J$ = 5 Hz, $CH_3$, H), $\delta$ 3.45 (m, CH, 1H), $\delta$ 4.17 (m, $CH_2$, 6H), $\delta$ 4.78 (dt, $J$ = 48 Hz CHF, 1H).

4-Fluoro-1-phenylhexane-1,5-dione **(9)** $^1$H NMR $\delta$ 2.29 (d, $J$ = 5 Hz, $CH_3$ 3H), 2.0 (m, $CH_2$, 2H), $\delta$ 2.4 (m, $CH_2$, 2H), 4.80 (dm, $J$ = 5 8 Hz, CHF, 1H), 7.25–7.9 (m, 5H aromatic).

3-Fluoro-4-(4-hydroxyphenyl)butan-2-one **(11)** raspberry odor, $^1$H NMR $\delta$ 2.15 (d, $J$ = 5 Hz, $CH_3$, 3H), 2.95–3.14 (m, $CH_2$, 2H), 4.2 (OH), 4.94 (dm, $J_{HF}$ = 50 Hz, CHF), 6.79, 7.15 (dd, $J$ = 9 Hz, CH, 4H aromatic); $^{13}$C NMR $\delta$ 26.8 (d, $J$ = 9 Hz, $CH_3$), 37.54 (d, $J$ = 21 Hz, $CH_2$), 96.1 (d, $J$ = 187 Hz, CFH), 117.0, 123.7, 131.2, 155.4 (aromatic), 208.6 (d, $J$ = 27 Hz, CO).

3-Fluoro-4-(4-hydroxy-2,6-dimethyl-phenyl)-butan-2-one **(13)** mp 105–109 °C, $^1$H NMR $\delta$ 2.29 (d, $J$ = 5 Hz, $CH_3$, 3H), 2.30 (s, $CH_3$, 6H), 3.10 (m, $CH_2$, 2H), 4.41 (dm, $J_{HF}$ = 50 Hz, CHF, 1H), 4.73 (OH), 6.54 (s, aromatic, 2H) $^{13}$C NMR) $\delta$ 20.6 (t, $J$ = 3 Hz, $2CH_3$), 26.0

(d, $J$ = 3 Hz, $CH_3$), 31.4 (d, $J$ = 21 Hz, $CH_2$), $\delta$ 96.4 (d, $J$ = 187 Hz, CHF), 118.0, 118.5 123.5, 139.8, (s, aromatic), 154.3 (s, COH), $\delta$ 208.4 (d, $J$ = 26 Hz, CO).

3-Fluoro-4-(4-hydroxy-naphthalen-1-yl)butan-2-one **(15)** raspberry odor, $^1$H NMR $\delta$ 2.20 (d, $J$ = 5 Hz, $CH_3$, 3H), 3.5 (dm, $CH_2$ 2H), 5.06 (dm, $J_{HF}$ = 50 Hz, CHF) 6.75–8.35 (m, aromatic, 6H); $^{13}$C NMR ($CDCl_3$, TMS) 26.5 (s, $CH_3$), 35.5 (d, $J$ = 21 Hz, $CH_2$), 96.7 (d, $J$ = 159 Hz, CHF), 108.9, 122.1, 123.3, 124.0, 126.3, 128.0 133.5 (aromatic), 152.0 (s, COH), 210 (d, $J$ = 26 Hz, CO).

3-Ethoxy-2-fluoro-2,3-dihydro-3-methyl-1H-benzo[f]chromene **(17)** $^1$H NMR $\delta$ 1.01 (t, $J$ = 7 Hz, $CH_3$, 3H), 1.76 (d, $J$ = 2 Hz, $CH_3$, 3H), 3.45 (m, $CH_2$,2H), 3.68 (q, $OCH_2$, 2H), 4.85 (m, $J_{HF}$ = 50 Hz, CHF, 1H), 7.14–7.85 (m, aromatic, 6H); $^{13}$C NMR $\delta$ 15.63 (d, $J$ = 4 Hz, $CH_3$), $\delta$ 19.8 (d, $J$ = 9 Hz, $CH_3$), 25.5 (d, $J$ = 21 Hz, $CH_2$), 57.1 (s, $OCH_2$), 83.5 (d, CHF), 97.8 (d. J = 3 Hz, OCO), 111.2, 119.1. 123.0, 124.1, 128.3. 129.5, 130.0, 131.3, 133.2, 133.7.0 (aromatic), 148.8 (s, C–O).

## Acknowledgment

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