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### THE SYNTHESIS OF FLUOROHETEROCYCLIC KETENE AMINALS

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## THE SYNTHESIS OF FLUOROHETEROCYCLIC KETENE AMINALS

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### ABSTRACT

The synthesis of fluoroheterocyclic ketene amins was investigated. Fluorobenzyl ketene dithioacetals **1c** reacted with nitric acid in the presence of concentrated sulfuric acid to give compound **2c**. **1** reacted with diamines to afford **3–4**. *C*-fluorobenzoylation of **3–4** give the corresponding **5–8**.

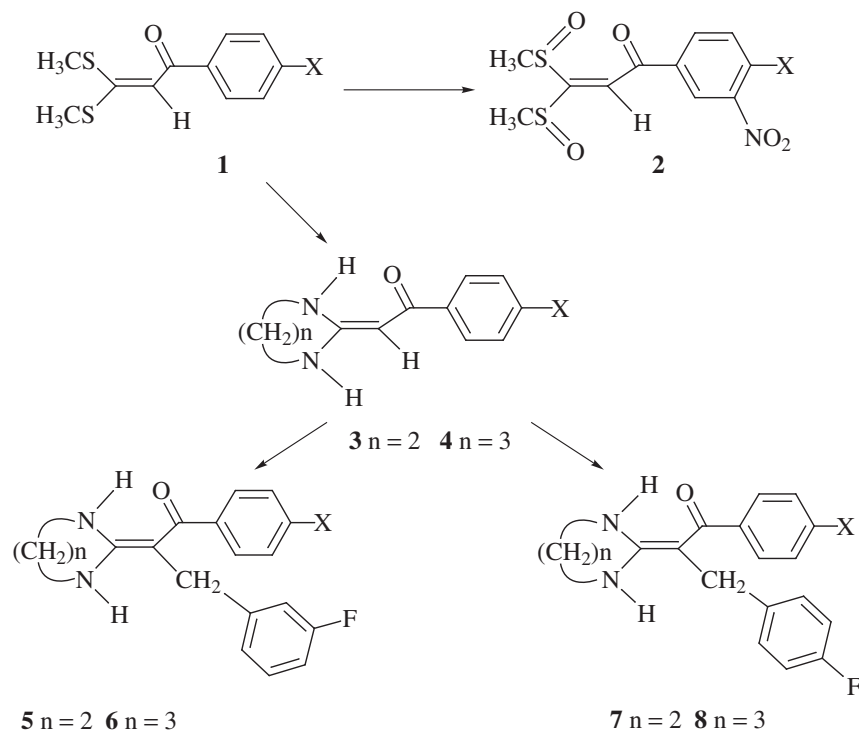
The synthesis and reactions of heterocyclic ketene amins have attracted the interest of organic chemists because these compounds are important intermediates for the synthesis of a wide variety of new heterocycles and fused heterocycles (1–10). Certain ketene amins have antiviral activity (11,12); however, the synthesis of fluoroheterocyclic analogs has not yet been reported. In this paper, we disclose methods for the synthesis of fluoroheterocyclic ketene amins.

Ketene dithioacetals **1** were prepared by the acetophenones with sodium hydride and carbon disulfide, followed by methyl iodide according to a literature method (13). Fluorobenzyl ketene dithioacetals **1c** (8) reacted with 90%

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nitric acid in the presence of concentrated sulfuric acid at  $-5^{\circ}\text{C}$  to give 1-(4'-fluoro-3'-nitro-phenyl)-3,3-bis-methanesulfinyl-propenone **2c** by oxidation and nitration reaction sequence. (**1c** spectra data:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.93 (d,  $J=10\text{Hz}$ , 2H), 7.09 (d,  $J=9.9\text{ Hz}$ , 2H), 6.71(s, 1H), 2.55 (s, 3H), 2.52 (s, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  183.9, 166.8, 162.5, 135.0, 130.1, 129.9, 115.5, 115.1, 109.0, 17.2, 14.9. Anal. calcd. for  $\text{C}_{11}\text{H}_{11}\text{FOS}_2$  (242.33): C, 54.52; H, 4.58. Found: C, 54.52; H, 4.61.) **1** reacted readily with diamines in anhydrous toluene to give compounds **3–4**. Fluorobenzoylation of **3–4** only afforded C-alkylation products **5–8** (see Scheme 1). The reaction conditions, yields, and melting points of **2–8** are listed in Table 1.



1–8	a	b	c
X	H	Cl	F

Scheme 1.



**Table 1.** Compounds **2–8** Prepared

Products	Reaction Conditions		Yield (%)	Mp (°C)
	Temp (°C)	Time (h)		
<b>2c</b>	−5	1	75	109–111
<b>3c</b>	110	3	89	224–225
<b>4c</b>	110	2	91	228–230
<b>5c</b>	70	4	68	171–173
<b>6a</b>	60	2	93	150–151
<b>6b</b>	65	3	90	220–222
<b>6c</b>	65	2	94	170–172
<b>7b</b>	50	5	78	186–188
<b>8a</b>	50	1	92	135–137
<b>8b</b>	50	1.5	81	112–114
<b>8c</b>	50	2	77	160–161

The structures of **2–8** were established by spectroscopic data. In IR spectra of **2c**, a nitro group absorption at ca. 1520 cm<sup>−1</sup> and ca. 1340 cm<sup>−1</sup> indicated that aromatic nitration and oxidation of the methylsulfanyl group occurred in the reaction of **1c** with nitric acid-sulfuric acid. The <sup>1</sup>H and <sup>13</sup>C NMR spectra also confirmed these aspects. In IR spectra of **3–8**, there was an NH stretching absorption band at ca. 3400 cm<sup>−1</sup> and a very strong carbonyl absorption of the aroyl group of **3–8** at ca. 1615 cm<sup>−1</sup>. In the <sup>1</sup>H NMR spectra, the signals of two nitrogen protons (9.25–11.04 ppm) and one ethylenic proton (5.15–5.24 ppm) of **3–4** were discovered, the signals of two nitrogen protons of **5–8** were shown to still exist at 10.33–11.25 ppm. These data exclude either the *N*-alkylation or *O*-alkylation of **3–4**. Furthermore, the ethylenic proton signal of **5–8** disappeared, indicating that the fluorobenzoylation took place at the ethylenic position of **3–4**.

## EXPERIMENTAL

### General Methods

Melting points were uncorrected. All reagents and solvents were obtained from Aldrich, Acros, Fisher, or VWR. Reaction progress was monitored by analytical thin-layer chromatography (Analtech scored 2.5 cm × 10 cm hard TLC plates, glass). Silica gel used in flash chromatography was 60–200 mesh. Infrared spectra were measured with an Avatar 360 ESP spectrometer and are expressed in reciprocal centimeters. <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra were obtained on a Bruker



200-MHz spectrometer. The chemical shifts were reported in ppm downfield from Me<sub>4</sub>Si. J values are given in Hz.

1-(4'-Fluoro-3'-nitro-phenyl)-3,3-bis-methanesulfinyl-propenone (**2c**)

Fluorobenzoyl ketene dithioacetals **1c** (485 mg, 2 mmol) was added in portions to a well-stirred solution of 90% nitric acid (8 mL) and 98% sulfuric acid (10 mL) at  $-5^{\circ}\text{C}$  over a 1-h period. After stirring for a further 30 min, chloroform (100 mL) was added. Then ice water (50 mL) was added dropwise. The organic phase was separated, dried (MgSO<sub>4</sub>), and filtered. The solvent was removed under reduced pressure to afford **2c** as an oil, which was purified by flash chromatography (chloroform-methanol, 25:1) to yield **2c** (630 mg, 75%) as yellow needles, mp  $109^{\circ}\text{--}111^{\circ}\text{C}$ ; IR (KBr): 3428 (NH), 1645 (CO), 1594, 1571, 1520, 1340, 1058, 1022  $\text{cm}^{-1}$ ; <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  8.13 (m, 1H), 8.04 (s, 1H), 7.24 (m, 1H), 7.17 (s, 1H), 3.19 (s, 3H), 3.14 (s, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  185.7, 176.7, 169.2, 164.1, 132.1, 131.9, 125.4, 116.7, 116.3, 45.7, 43.2. Anal. calcd. for C<sub>13</sub>H<sub>18</sub>FN<sub>2</sub>O<sub>5</sub>S<sub>2</sub> (351.42): C, 44.43; H, 5.16; N, 3.99. Found: C, 44.80; H, 5.06; N, 3.97.

General Procedure for the Synthesis of Compounds **3** and **4**

A solution of ketene dithioacetals **1** (8 mmol) and the corresponding diamines (10 mmol) in toluene (50 mL) was heated at reflux for 3 h, whereupon, a white solid precipitated. The precipitate was filtered, washed with cold acetone, and dried under vacuum. Spectra data corresponding to **3** and **4** are given below.

1-(4'-Fluoro-phenyl)-2-imidazolidin-2-ylidene-ethanone **3c**

Yield 89%; mp  $224^{\circ}\text{--}225^{\circ}\text{C}$ ; IR (KBr): 3420 (NH), 3163, 1615 (CO), 1587, 1551, 922, 850  $\text{cm}^{-1}$ ; <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  9.25 (s, 2H), 7.76 (m, 2H), 7.17 (d,  $J = 8.9$  Hz, 2H), 5.24 (s, 1H), 3.49 (m, 4H); <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  180.0, 165.9, 161.1, 131.4, 130.5, 127.2, 116.8, 113.4, 74.8, 43.1, 42.4. Anal. calcd. for C<sub>11</sub>H<sub>11</sub>FN<sub>2</sub>O (206.22): C, 64.07; H, 5.38; N, 13.58. Found: C, 64.17; H, 5.37; N, 13.42.

1-(4'-Fluoro-phenyl)-2-(tetrahydro-pyrimidin-2'-ylidene)-ethanone **4c**

Yield 91%; mp  $228^{\circ}\text{--}230^{\circ}\text{C}$ ; IR (KBr): 3455 (NH), 3196, 1610 (CO), 1597, 1530, 1150, 845  $\text{cm}^{-1}$ ; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>):  $\delta$  11.07 (s, 2H), 7.68 (m, 2H), 7.15 (m, 2H), 5.15 (s, 1H), 3.28 (t, 4H), 1.82 (m, 2H); <sup>13</sup>C NMR (DMSO-d<sub>6</sub>):  $\delta$  178.5,



165.4, 160.5, 138.9, 128.3, 128.1, 114.9, 114.5, 76.7, 37.8(2C), 20.5. Anal. calcd. for  $C_{12}H_{13}FN_2O$  (220.24): C, 65.44; H, 5.95; N, 12.72. Found: C, 65.24; H, 5.95; N, 12.68.

### General Procedure for the Synthesis of Compounds 5–8

To a mixture of **3** or **4** (1 mmol) in toluene (15 mL) was added fluorobenzyl chloride (1.5 mmol), then the reaction mixture was heated at 50°–70°C for 1–5 h until no starting material **3** or **4** was detected by TLC ( $CHCl_3$ :  $CH_3OH$ , 10: 1). The solvent was removed under reduced pressure. The crude product was purified by flash silica gel chromatography ( $CHCl_3$ :  $CH_3OH$ , 50: 1) to give the corresponding product (see Table 1). Spectra data of **5–8** are given below.

#### 3-(3'-Fluoro-phenyl)-1-(4'-fluoro-phenyl)-2-imidazolidin-2-ylidene-propan-1-one **5c**

Yield 68%; mp 171°–173°C; IR (KBr): 3405 (NH), 3126, 1692 (CO), 1614, 1588, 1092, 947, 839  $cm^{-1}$ ;  $^1H$  NMR (DMSO- $d_6$ ):  $\delta$  11.25 (s, 2H), 7.10–8.24 (m, 8H), 3.48 (m, 4H), 3.20 (s, 2H);  $^{13}C$  NMR (DMSO- $d_6$ ):  $\delta$  192.5, 167.6, 164.3, 139.4, 133.0, 132.8, 132.3, 131.2, 131.1, 125.6, 117.1, 116.3, 114.6, 114.4, 46.9, 44.9(2C), 36.5. Anal. calcd. for  $C_{18}H_{16}F_2N_2O$  (314.33): C, 68.78; H, 5.13; N, 8.91. Found: C, 68.86; H, 5.22; N, 8.98.

#### 3-(3'-Fluoro-phenyl)-1-phenyl-2-(tetrahydro-pyrimidin-2'-ylidene)-propan-1-one **6a**

Yield 93%; mp 150°–151°C; IR (KBr): 3426 (NH), 3109, 1685 (CO), 1615, 1586, 1314, 948  $cm^{-1}$ ;  $^1H$  NMR (DMSO- $d_6$ ):  $\delta$  10.41 (s, 2H), 7.03–8.29 (m, 9H), 3.37 (m, 4H), 3.21 (s, 2H), 1.58 (m, 2H);  $^{13}C$  NMR (DMSO- $d_6$ ):  $\delta$  193.8, 164.8, 159.4, 139.7, 135.4, 134.4, 130.4, 130.3, 129.2, 125.5, 116.3, 115.8, 114.1, 113.7, 50.9, 39.2(2C), 34.8, 17.7. Anal. calcd. for  $C_{19}H_{19}FN_2O$  (310.37): C, 73.53; H, 6.17; N, 9.03. Found: C, 73.04; H, 6.17; N, 9.06.

#### 1-(4'-Chloro-phenyl)-3-(3'-fluoro-phenyl)-2-(tetrahydro-pyrimidin-2'-ylidene)-propan-1-one **6b**

Yield 90%; mp 220°–222°C; IR (KBr): 3400 (NH), 3129, 1692 (CO), 1614, 1588, 1319, 947, 836  $cm^{-1}$ ;  $^1H$  NMR (DMSO- $d_6$ ):  $\delta$  10.42 (s, 2H), 8.20 (d,  $J = 9.0$  Hz, 2H), 7.60 (d,  $J = 9.2$  Hz, 2H), 7.04–7.37 (m, 4H), 3.37 (m, 4H), 3.21 (s, 2H), 1.57 (m, 2H);  $^{13}C$  NMR (DMSO- $d_6$ ):  $\delta$  193.6, 164.8, 159.4, 139.5, 134.0,



131.0, 130.5, 129.3, 130.3, 125.5, 116.3, 115.9, 114.2, 113.7, 50.9, 39.1(2C), 34.8, 17.7. Anal. calcd. for  $C_{19}H_{18}ClFN_2O$  (344.81): C, 66.18; H, 5.26; N, 8.12. Found: C, 66.06; H, 5.02; N, 8.15.

3-(3'-Fluoro-phenyl)-1-(4'-fluoro-phenyl)-2-(tetrahydro-pyrimidin-2'-ylidene)-propan-1-one **6c**

Yield 94%; mp  $170^{\circ}$ – $172^{\circ}C$ ; IR (KBr): 3400 (NH), 3129, 1689 (CO), 1610, 1588, 1320, 945, 845  $cm^{-1}$ ;  $^1H$  NMR (DMSO- $d_6$ ):  $\delta$  10.43 (s, 2H), 8.20 (d,  $J = 8.8$  Hz, 2H), 7.66 (d,  $J = 9.2$  Hz, 2H), 7.00–7.47 (m, 4H), 3.39 (m, 4H), 3.21 (s, 2H), 1.58 (m, 2H);  $^{13}C$  NMR (DMSO- $d_6$ ):  $\delta$  193.8, 168.9, 165.2, 163.8, 159.4, 140.1, 132.7, 132.6, 130.6, 125.9, 116.9, 116.3, 114.6, 114.1, 51.2, 39.2(2C), 35.4, 18.1. Anal. calcd. for  $C_{19}H_{18}F_2N_2O$  (328.36): C, 69.50; H, 5.53; N, 8.53. Found: C, 69.87; H, 5.22; N, 8.51.

1-(4'-Chloro-phenyl)-3-(4'-fluoro-phenyl)-2-imidazolidin-2-ylidene-propan-1-one **7b**

Yield 78%; mp  $186^{\circ}$ – $188^{\circ}C$ ; IR (KBr): 3410 (NH), 3034, 1682 (CO), 1586, 1402, 1091, 949, 848  $cm^{-1}$ ;  $^1H$  NMR (DMSO- $d_6$ ):  $\delta$  10.86 (s, 2H), 7.58–8.22 (m, 4H), 7.03–7.33 (m, 4H), 3.75 (m, 4H), 3.31 (s, 2H);  $^{13}C$  NMR (DMSO- $d_6$ ):  $\delta$  193.3, 166.9, 164.7, 139.7, 133.7, 131.1, 130.6, 130.4, 129.3, 125.3, 116.2, 115.8, 114.2, 113.8, 46.6, 44.4(2C), 34.7. Anal. calcd. for  $C_{18}H_{16}ClFN_2O$  (330.78): C, 65.36; H, 4.88; N, 8.47. Found: C, 65.81; H, 4.63; N, 8.42.

3-(4'-Fluoro-phenyl)-1-phenyl-2-(tetrahydro-pyrimidin-2'-ylidene)-propan-1-one **8a**

Yield 92%; mp  $135^{\circ}$ – $137^{\circ}C$ ; IR (KBr): 3426 (NH), 3127, 1690 (CO), 1615, 1588, 1319, 947  $cm^{-1}$ ;  $^1H$  NMR (DMSO- $d_6$ ):  $\delta$  10.33 (s, 2H), 7.55–8.24 (m, 4H), 7.00–7.38 (m, 5H), 3.34 (m, 4H), 3.21 (s, 2H), 1.59 (m, 2H);  $^{13}C$  NMR (DMSO- $d_6$ ):  $\delta$  194.7, 164.7, 159.6, 139.7, 135.4, 134.4, 130.4, 130.3, 129.2, 125.5, 116.3, 115.8, 114.1, 113.7, 50.8, 39.2(2C), 34.9, 17.7. Anal. calcd. for  $C_{19}H_{19}FN_2O$  (310.37): C, 73.53; H, 6.17; N, 9.03. Found: C, 73.80; H, 6.10; N, 9.00.

1-(4'-Chloro-phenyl)-3-(4'-fluoro-phenyl)-2-(tetrahydro-pyrimidin-2'-ylidene)-propan-1-one **8b**

Yield 81%; mp  $112^{\circ}$ – $114^{\circ}C$ ; IR (KBr): 3407 (NH), 3129, 1687 (CO), 1610, 1575, 1319, 945  $cm^{-1}$ ;  $^1H$  NMR (DMSO- $d_6$ ):  $\delta$  10.48 (s, 2H), 7.83–8.52 (m, 4H),



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7.08–7.65 (m, 4H), 3.36 (m, 4H), 3.21 (s, 2H), 1.61 (m, 2H);  $^{13}\text{C}$  NMR (DMSO- $d_6$ ):  $\delta$  193.7, 163.5, 159.1, 139.1, 133.7, 132.6, 132.5, 130.9, 130.6, 128.8, 115.1, 114.7, 114.1, 113.7, 50.8, 39.2(2C), 34.0, 17.3. Anal. calcd. for  $\text{C}_{19}\text{H}_{18}\text{ClFN}_2\text{O}$  (344.81): C, 66.18; H, 5.26; N, 8.12. Found: C, 66.50; H, 5.09; N, 8.15.

### 1,3-Bis-(4'-fluoro-phenyl)-2-(tetrahydro-pyrimidin-2'-ylidene)-propan-1-one **8c**

Yield 77%; mp  $160^\circ\text{--}161^\circ\text{C}$ ; IR (KBr): 3400 (NH), 3120, 1685 (CO), 1612, 1578, 1317, 940  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  10.40 (s, 2H), 7.10–8.42 (m, 8H), 3.35 (m, 4H), 3.21 (s, 2H), 1.62 (m, 2H);  $^{13}\text{C}$  NMR (DMSO- $d_6$ ):  $\delta$  194.0, 168.9, 164.3, 163.6, 159.5, 133.4, 132.8, 132.6, 131.8, 131.5, 116.9, 116.5, 115.9, 115.5, 51.5, 39.1(2C), 35.0, 18.1. Anal. calcd. for  $\text{C}_{19}\text{H}_{18}\text{F}_2\text{N}_2\text{O}$  (328.36): C, 69.50; H, 5.53; N, 8.53. Found: C, 69.57; H, 5.17; N, 8.74.

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