Expedient Synthesis of 5-Benzoylpyrimidine-2,4-diones from Baylis-Hillman Adducts

Jeong Mi Kim, Eun Sun Kim, and Jae Nyoung Kim*

Department of Chemistry and Institute of Basic Science, Chonnam National University, Gwangju 500-757, Korea
E-mail: kimjn@chonnam.ac.kr
Received November 7, 2008, Accepted February 6, 2009

Key Words: Baylis-Hillman adducts, Pyrimidine-2,4-diones, PCC oxidation

The synthesis and modification of pyrimidine-2,4-dione (uracil) derivatives has received much attention due to their importance in nucleic acid chemistry as well as in synthetic organic chemistry.1-3 Most of the modifications involved the introduction of various substituents at the 5- or 6-position of uracil ring.1,2 Recently numerous chemical transformations of Baylis-Hillman adducts have been published involving the synthesis of various heterocyclic compounds.3-5

The synthesis of 5-benzyluracil 2a starting from Baylis-Hillman adduct was reported by us recently.5 5-Benzoyluracil and related compounds are also important,1a,b,2 thus we examined the oxidation of 5-benzyluracil 2a into 5-benzoyl derivative 4a as in Scheme 1. The reaction of 2a with SeO2 or KMnO4 showed no reaction while with PCC (pyridinium chlorochromate) or CrO3/AcOH produced low yield of product.6

Thus we decided to prepare 4a by the oxidation of 5-benzylideneuracil derivative 3a with PCC, which was efficiently used for the oxidation of similar compounds by us recently.7 As reported, 5-benzyl derivative 2a was obtained from 1a with strong base such as NaOEt or t-BuOK.5 When the reaction of 1a was carried out under the influence of K2CO3 in DMF at elevated temperature, 5-benzyl derivative 2a was the major product again. Fortunately, 5-benzylidene compound 3a was obtained as the major product (82%) when we run the reaction under the influence of a catalytic amount of K2CO3 (0.2 equiv) in DMF at room temperature. With this benzylidene compound 3a, we examined the PCC oxidation and obtained the benzoyl derivative 4a in good yield (78%). Encouraged by the results we prepared 3b-f and examined the oxidation to 5-benzoyluracils 4b-f and the results are summarized in Scheme 2 and Table 1.

The synthesis of starting materials 1b-f was carried out as reported.5 Cyclization of 1b-e was carried out under the same conditions (K2CO3, DMF, rt, 8 h), and we obtained 3b-e in 63-92% yields. However, 5-benzyl derivative was formed as the major product when we run the reaction of thiourea derivative 1f under the same conditions even at room temperature presumably by the base-mediated isomerization process of 3f. Thus we carried out the reaction in water without base at refluxing temperature for long time for the synthesis of 3f. With these benzylidene compounds 3b-f, the following oxidation was carried out with PCC (2.0 equiv) in CH2Cl2 at refluxing temperature to obtain 4b-g in 63-80% yields. As in entries 1-4, N-substituents (R1 and R2) did not affect the reactivity and the reactions with hexylidene

Scheme 1

Scheme 2
derivative (entry 5) and thiourea derivative (entry 6) also showed some reactivity.

In summary, we developed an efficient way for the preparation of 5-benzoylpyrimidine-2,4-dione derivatives from Bayliss-Hillman adducts by using PCC oxidation of 5-benzoylpyrimidine derivatives as the key step.

**Experimental Section**

Synthesis of starting materials was carried out as reported and the spectroscopic data of unknown compounds, 1b, 1e, and 1f, are as follows. Compounds 1a-d and 1f were obtained as pure E isomers, but compound 1e was separated as an E/Z mixture (E/Z = 4:1). However, compound 3e (E form) could be isolated in pure state from the corresponding Z-3e derived from the minor Z-1e.

**Table 1. Synthesis of 5-benzylidene- and 5-benzoyl pyrimidines**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Conditionsa</th>
<th>Compound 3 (%)</th>
<th>Product 4 (%)b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>A</td>
<td>3a(82)</td>
<td>4a(78)</td>
</tr>
<tr>
<td>2</td>
<td>1b</td>
<td>A</td>
<td>3b(92)</td>
<td>4b(73)</td>
</tr>
<tr>
<td>3</td>
<td>1c</td>
<td>A</td>
<td>3c(90)</td>
<td>4c(63)</td>
</tr>
<tr>
<td>4</td>
<td>1d</td>
<td>A</td>
<td>3d(90)</td>
<td>4d(80)</td>
</tr>
<tr>
<td>5</td>
<td>1e</td>
<td>A</td>
<td>3e(63)</td>
<td>4e(65)</td>
</tr>
<tr>
<td>6</td>
<td>1f</td>
<td>B</td>
<td>3f(64)</td>
<td>4f(66)</td>
</tr>
</tbody>
</table>

aConditions: A: K₂CO₃ (0.2 equiv), DMF, rt, 8 h; Conditions B: H₂O, reflux, 48 h. bConditions: PCC (2.0 equiv), CH₂Cl₂, reflux, 8 h.

**Typical procedure for the synthesis of 3a.** A mixture of 1a (207 mg, 0.5 mmol) and K₂CO₃ (14 mg, 0.1 mmol) in CH₂Cl₂ (5 mL) was stirred at room temperature for 8 h. After the usual aqueous workup and column chromatographic purification process (hexanes/ether, 1:1) compound 3a was obtained as a white solid, 157 mg (82%). Other compounds were synthesized similarly and their spectroscopic data are as follows.

**Compound 3a:** 82% white solid, mp 122-124 °C; IR (KBr) 1699, 1667, 1216 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 4.23 (d, J = 2.4 Hz, 2H), 4.65 (s, 2H), 7.14-7.17 (m, 2H), 7.23-7.40 (m, 11H), 7.46-7.50 (m, 2H), 7.84 (t, J = 2.4 Hz, 1H); ¹³C NMR (CDCl₃, 75 MHz) δ 46.42, 46.63, 51.65, 122.82, 127.28, 127.84, 128.01, 128.36, 128.73, 128.74, 128.82, 129.42, 129.70, 134.03, 135.94, 138.88, 138.80, 152.71, 163.91; ESIMS m/z 383 (M⁺+H).

**Compound 3b:** 92% white solid, mp 198-200 °C; IR (KBr) 1713, 1678, 1225 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 4.87 (d, J = 2.1 Hz, 2H), 7.21-7.49 (m, 15H), 7.99 (t, J = 2.1 Hz, 1H); ¹³C NMR (CDCl₃, 75 MHz) δ 47.96, 122.95, 125.62, 126.93, 128.28, 128.82 (2C), 128.90, 129.09, 129.69, 129.85, 133.78, 135.75, 137.94, 141.42, 151.99, 164.20.

**Compound 3c:** 90% white solid, mp 185-187 °C; IR (KBr) 3200, 1699, 1261 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 4.29 (d, J = 2.1 Hz, 2H), 4.65 (s, 2H), 7.18-7.43 (m, 10H), 7.86 (t, J = 2.1 Hz, 1H), 8.04 (s, 1H); ¹³C NMR (CDCl₃, 75 MHz) δ 45.52, 50.57, 122.05, 127.96, 128.08, 128.83, 128.89, 129.73, 129.92, 133.78, 135.70, 139.24, 151.69, 163.98.

**Compound 3d:** 90% white solid, mp 295-297 °C (dec.); IR (KBr) 3149, 1682, 1573 cm⁻¹; ¹H NMR (DMSO-d₆, 300 MHz) δ 4.80 (d, J = 7.2 Hz, 2H), 7.24-7.31 (m, 1H), 7.37-7.47 (m, 9H), 7.74 (t, J = 7.2 Hz, 1H), 10.70 (s, 1H); ¹³C NMR (DMSO-d₆, 75 MHz) δ 48.59, 123.68, 125.96, 126.46, 128.84, 128.89, 129.58, 130.17, 133.75, 136.64, 141.58, 151.14, 164.01; ESIMS m/z 279 (M⁺+H).

**Compound 3e:** 63%; colorless oil; IR (film) 1704, 1666, 1453 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 0.85 (t, J = 7.2 Hz, 3H), 1.15-1.43 (m, 6H), 2.12 (q, J = 7.5 Hz, 2H), 4.00 (2H), 4.37 (d, J = 7.5 Hz, 1H), 7.15-7.33 (m, 10H); ¹³C NMR (major + minor, CDCl₃, 75 MHz) δ 13.76, 13.84, 22.22, 22.25, 28.34, 28.49, 28.66, 29.33, 31.24, 31.34, 42.15, 44.81, 44.91, 48.78, 49.26, 49.56, 51.36, 51.90, 126.49, 126.75, 126.89, 126.92, 127.07, 127.34, 127.39, 127.52, 127.72, 127.84, 128.31, 128.37, 128.44, 137.87, 138.00, 139.57, 139.71, 146.47, 147.66, 158.36, 158.99, 167.51, 167.36 (1C is overlapped).

**Compound 1f:** 96%; colorless oil; IR (film) 3411, 3304, 1713, 1697, 1257, 1202 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 3.68 (s, 3H), 4.50 (s, 2H), 4.83 (d, J = 4.8 Hz, 2H), 4.90 (s, 2H), 6.89-6.92 (m, 2H), 6.99-7.01 (m, 2H), 7.04-7.11 (m, 3H), 7.17-7.33 (m, 9H), 7.81 (s, 1H); ¹³C NMR (CDCl₃, 75 MHz) δ 43.95, 50.09, 52.14, 53.51, 126.51, 126.81, 126.85, 127.29, 127.42, 127.77, 128.08, 128.31, 128.58, 128.85, 133.14, 136.11, 137.84, 143.75, 167.96, 183.95.
their spectroscopic data are as follows.

**Compound 4a**: 78%; white solid, mp 115-117 °C; IR (KBr) 1716, 1673, 1605, 1448 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 4.97 (s, 2H), 5.13 (s, 2H), 7.21-7.40 (m, 10H), 7.44-7.54 (m, 3H), 7.67-7.69 (m, 2H), 7.88 (s, 1H); ¹³C NMR (CDCl₃, 75 MHz) δ 44.71, 53.06, 113.33, 127.75, 128.03, 128.25, 128.37, 128.76, 129.11, 129.15, 129.22, 132.89, 134.42, 136.24, 137.41, 147.75, 150.89, 160.03, 190.68; ESIMS m/z 397 (M+H).

**Compound 4b**: 73%; white solid, mp 239-241 °C; IR (KBr) 3163, 1709, 1305 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 7.26-7.31 (m, 2H), 7.36-7.57 (m, 11H), 7.80-7.84 (m, 2H), 4.97 (s, 2H), 5.13 (s, 2H), 7.21-7.40 (m, 10H), 7.44-7.54 (m, 3H), 1.26-1.35 (m, 4H), 1.55-1.67 (m, 2H), 3.03 (t, J = 7.2 Hz, 2H), 4.98 (s, 2H), 5.15 (s, 2H), 7.23-7.40 (m, 8H), 7.44-7.48 (m, 2H), 8.21 (s, 1H); ¹³C NMR (CDCl₃, 75 MHz) δ 13.90, 22.48, 23.40, 31.35, 42.58, 44.81, 53.35, 112.16, 127.76, 128.22, 128.45, 128.80, 128.89, 134.44, 136.30, 148.33, 150.97, 160.55, 197.06; ESIMS m/z 413 (M+H).

**Acknowledgments.** This work was supported by the Korea Research Foundation Grant funded by the Korean Government (MOEHRD, KRF-2007-313-C00417). Spectroscopic data was obtained from the Korea Basic Science Institute, Gwangju branch.

References and Notes


6. The oxidation of 2a with PCC (4.0 equiv)/CH₂Cl₂ (reflux, 72 h) afforded 19% of product 4a and 2a was recovered in 70%. The reaction of CrO₃ (5.0 equiv)/AcOH (reflux, 2 h) produced 4a in 27% Oxidation of 2a with SeO₂ (2.0 equiv)/EtOH (reflux, 24 h) or K₂MnO₄ (2.0 equiv)/aqueous CH₂Cl₂ (reflux, 24 h) was ineffective.