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

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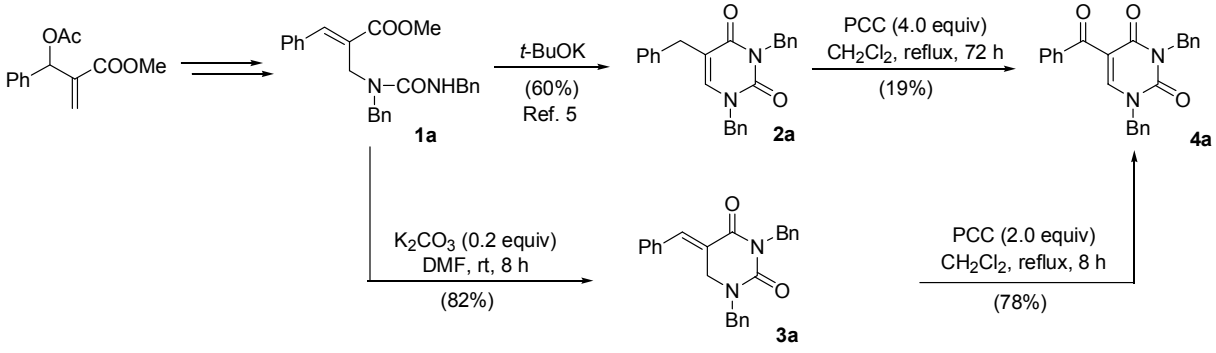
The synthesis and modification of pyrimidine-2,4-dione (uracil) derivatives has received much attention due to their importance in nucleic acid chemistry as well as in synthetic organic chemistry.[1-3] Most of the modifications involved the introduction of various substituents at the 5- or 6-position 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]

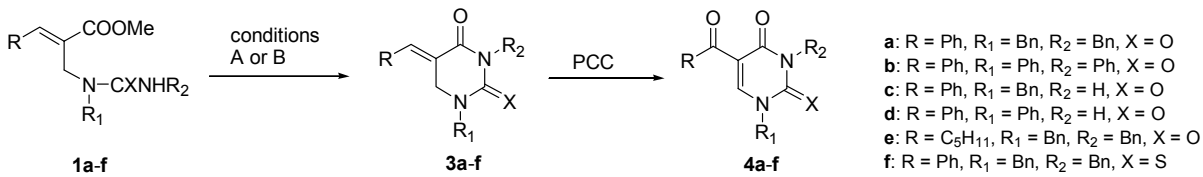
The synthesis of 5-benzyluracil **2a** starting from Baylis-Hillman adduct was reported by us recently.[5] 5-Benzoyluracil and related compounds are also important,[1a,b,2] thus we examined the oxidation of 5-benzyluracil **2a** into 5-benzoyl derivative **4a** as in Scheme 1. The reaction of **2a** with SeO_2 or $KMnO_4$ showed no reaction while with PCC (pyridinium chlorochromate) or CrO_3/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 K_2CO_3 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 K_2CO_3 (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 (K_2CO_3, 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 CH_2Cl_2 at refluxing temperature to obtain **4b-g** in 63-80% yields. As in entries 1-4, *N*-substituents (R_1 and R_2) did not affect the reactivity and the reactions with hexylidene



Scheme 1



Scheme 2

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

Entry	Substrate **1**	Conditions[a]	Compound **3** (%)	Product **4** (%)[b]
1	**1a**	A	**3a**(82)	**4a**(78)
2	**1b**	A	**3b**(92)	**4b**(73)
3	**1c**	A	**3c**(90)	**4c**(63)
4	**1d**	A	**3d**(90)	**4d**(80)
5	**1e**	A	**3e**(63)	**4e**(65)
6	**1f**	B	**3f**(64)	**4f**(66)

[a]Conditions A: K_2CO_3 (0.2 equiv), DMF, rt, 8 h; Conditions B: H_2O, reflux, 48 h. [b]Conditions: PCC (2.0 equiv), CH_2Cl_2, reflux, 8 h.

derivative (entry 5) and thiourea derivative (entry 6) also showed same reactivity.

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

Experimental Section

Synthesis of starting materials was carried out as reported[5] 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**.

Compound **1b**: 80%; colorless oil; IR (film) 3424, 1716, 1681 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.73 (s, 3H), 4.98 (s, 2H), 6.35 (s, 1H), 6.95-7.07 (m, 3H), 7.13-7.37 (m, 12H), 7.71 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 44.12, 52.14, 119.28, 122.84, 128.26 (2C), 128.41, 128.75, 128.87, 129.13, 129.26, 129.82, 134.41, 138.87, 139.75, 143.43, 154.22, 168.16.

Compound **1e**: 94%; colorless oil; IR (film) 3358, 1716, 1645 cm^{-1}; ^1H NMR (major *E*, $CDCl_3$, 300 MHz) δ 0.86 (t, *J* = 6.9 Hz, 3H), 1.15-1.43 (m, 6H), 2.12 (q, *J* = 7.5 Hz, 2H), 3.67 (s, 3H), 4.11 (s, 2H), 4.42-4.50 (m, 4H), 6.20 (t, *J* = 5.1 Hz, 1H), 6.90 (t, *J* = 7.5 Hz, 1H), 7.15-7.33 (m, 10H); ^1H NMR (minor *Z*, $CDCl_3$, 300 MHz) δ 0.89 (t, *J* = 6.9 Hz, 3H), 1.15-1.43 (m, 6H), 2.43 (q, *J* = 7.2 Hz, 2H), 3.66 (s, 3H), 4.00 (s, 2H), 4.42-4.50 (m, 4H), 5.47 (t, *J* = 5.4 Hz, 1H), 6.01 (t, *J* = 7.5 Hz, 1H), 7.15-7.33 (m, 10H); ^{13}C NMR (major + minor, $CDCl_3$, 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, 127.77, 128.24, 128.31, 128.37, 128.44, 137.87, 138.00, 139.57, 139.71, 145.68, 147.66, 158.36, 158.99, 167.51, 168.36 (1C is overlapped).

Compound **1f**: 96%; colorless oil; IR (film) 3411, 3304, 1713, 1697, 1257, 1202 cm^{-1}; ^1H NMR ($CDCl_3$, 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); ^{13}C NMR ($CDCl_3$, 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.

Typical procedure for the synthesis of 3a. A mixture of **1a** (207 mg, 0.5 mmol) and K_2CO_3 (14 mg, 0.1 mmol) in DMF (3.0 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 ($CDCl_3$, 300 MHz) δ 4.23 (d, *J* = 2.4 Hz, 2H), 4.65 (s, 2H), 5.15 (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); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 44.62, 44.63, 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, 137.88, 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 ($CDCl_3$, 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); ^{13}C NMR ($CDCl_3$, 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, 139.74, 141.42, 151.99, 164.20.

Compound **3c**: 90%; white solid, mp 185-187 °C; IR (KBr) 3200, 1699, 1261 cm^{-1}; ^1H NMR ($CDCl_3$, 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); ^{13}C NMR ($CDCl_3$, 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, 1373 cm^{-1}; ^1H NMR (DMSO-d_6, 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); ^{13}C NMR (DMSO-d_6, 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 ($CDCl_3$, 300 MHz) δ 0.85 (t, *J* = 7.2 Hz, 3H), 1.15-1.43 (m, 6H), 1.96-2.03 (m, 2H), 3.88-3.90 (m, 2H), 4.66 (s, 2H), 5.09 (s, 2H), 6.90-6.97 (m, 1H), 7.21-7.37 (m, 8H), 7.42-7.46 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.85, 22.31, 27.76, 28.01, 31.31, 43.10, 44.34, 51.43, 122.70, 127.17, 127.79, 127.92, 128.29, 128.66, 128.78, 136.06, 137.98, 142.91, 153.05, 163.39.

Compound **3f**: 64%; white solid, mp 136-138 °C; IR (KBr) 1686, 1448, 1174 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.37 (d, *J* = 2.1 Hz, 2H), 5.31 (s, 2H), 5.80 (s, 2H), 7.03-7.06 (m, 2H), 7.22-7.35 (m, 11H), 7.43-7.46 (m, 2H), 7.79 (t, *J* = 2.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 46.93, 50.04, 58.61, 122.43, 127.08, 127.78, 127.94, 128.02, 128.30, 128.79, 128.87, 129.44, 129.58, 133.64, 135.07, 137.82, 139.88, 161.39, 181.18.

Typical procedure for the synthesis of 4a. A mixture of **3a** (153 mg, 0.4 mmol) and PCC (173 mg, 0.8 mmol) in CH_2Cl_2 (5 mL) was heated to reflux for 8 h. The reaction mixture was filtered through a Celite pad and washed with CH_2Cl_2. The filtrates and washings were combined and solvent was removed. After column chromatographic purification (hexanes/ether, 1:1) compound **4a** was obtained as a white solid, 124 mg (78%). Other compounds were synthesized similarly and

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 ($CDCl_3$, 300 MHz) δ 4.97 (s, 2H), 5.13 (s, 2H), 7.21-7.40 (m, 10H), 7.44-7.54 (m, 3H), 7.65-7.69 (m, 2H), 7.88 (s, 1H); ^{13}C NMR ($CDCl_3$, 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) 1722, 1681, 1659, 1259 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.26-7.31 (m, 2H), 7.36-7.57 (m, 11H), 7.80-7.84 (m, 2H), 8.16 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 114.30, 126.34, 128.20, 128.26, 128.98, 129.32, 129.40, 129.44, 129.69, 133.04, 134.42, 137.50, 138.42, 148.80, 150.36, 160.23, 190.69.

Compound **4c**: 63%; white solid, mp 192-193 °C; IR (KBr) 3188, 1694, 1452 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.00 (s, 2H), 7.30-7.43 (m, 7H), 7.52-7.58 (m, 1H), 7.70-7.74 (m, 2H), 7.95 (s, 1H), 8.77 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 52.15, 114.09, 128.13, 128.37, 128.97, 129.31, 129.39, 133.16, 134.29, 137.18, 150.01, 150.23, 160.20, 190.15.

Compound **4d**: 80%; white solid, mp 240-241 °C; IR (KBr) 3163, 1709, 1305 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.43-7.52 (m, 7H), 7.60-7.65 (m, 1H), 7.82-7.84 (m, 2H), 8.07 (s, 1H), 11.80 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 113.43, 127.01, 128.24, 128.71, 129.15, 129.31, 132.93, 137.64, 138.45, 149.60, 149.95, 161.32, 190.52; ESIMS *m*/*z* 293 (M^++H).

Compound **4e**: 65%; colorless oil; IR (film) 1715, 1688, 1662, 1449 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.88 (t, J = 6.9 Hz, 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); ^{13}C NMR ($CDCl_3$, 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, 129.17, 134.44, 136.30, 148.33, 150.97, 160.55, 197.06; ESIMS *m*/*z* 391 (M^++H).

Compound **4f**: 66%; white solid, mp 135-137 °C; IR (KBr) 1692, 1666, 1224 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.56 (s, 2H), 5.76 (s, 2H), 7.22-7.56 (m, 13H), 7.66-7.69 (m, 2H), 7.95 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 50.77, 59.26, 115.81, 127.58, 128.12, 128.18, 128.24, 128.59, 128.81, 129.19, 129.29, 133.24, 134.03, 135.49, 136.96, 146.71, 157.79, 177.96, 190.31; ESIMS *m*/*z* 413 (M^++H).

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References and Notes

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