Synthesis of 3-Benzyl- or 3-Benzoyl-7,8-dihydro-6*H*-chromene Derivatives Starting from Baylis-Hillman Adducts

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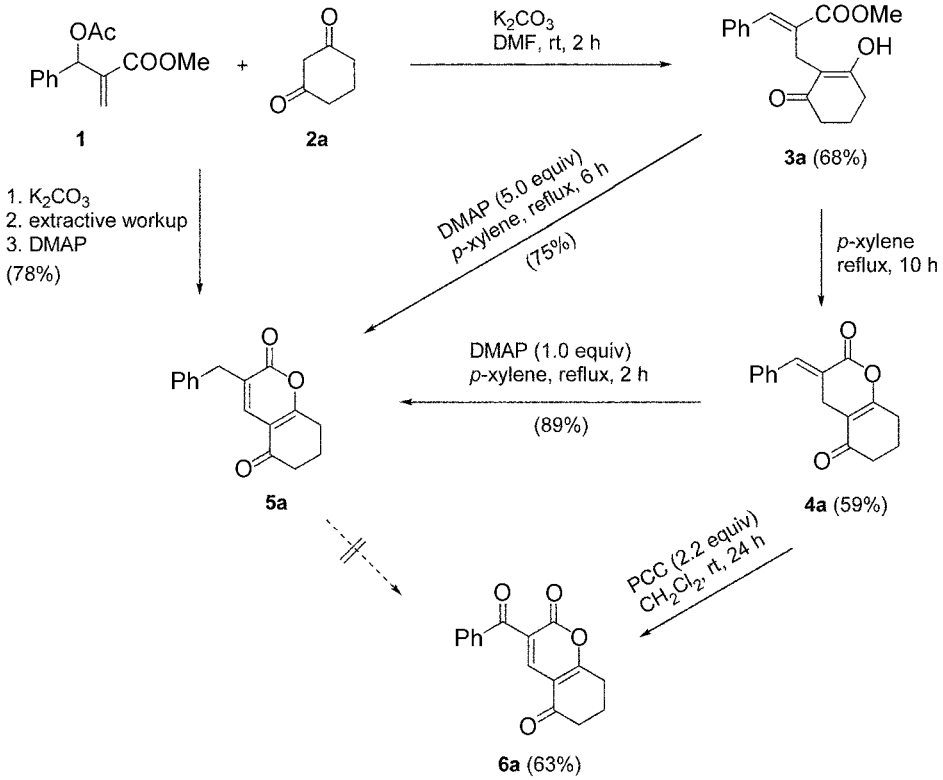
Recently, chemical transformations using the Baylis-Hillman adducts have been extensively investigated by us and other groups.[1] Among them, the reaction of Baylis-Hillman acetates and β-diketones or β-keto esters provided a variety of interesting compounds including alkylidene cyclohexenones,[2] 2-hydroxyacetophenones,[3] 3,4-dihydro-2*H*-pyrans,[4] 3-alkylidenebicyclo[3.2.1]octan-8-ones,[5] 4-arylidenecyclohexane-1,3-diones,[6] and 4-methylene-2-cyclohexenones.[7] Recently, 3-benzyl-2-hydroxy-7,8-dihydro-6*H*-quinolin-5-ones were synthesized from the reaction of Baylis-Hillman acetate and cyclic enaminone.[8]

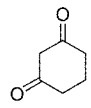
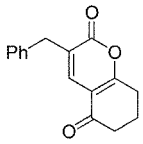
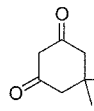
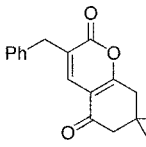
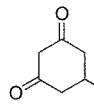
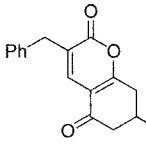
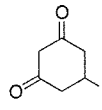
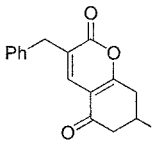
Various kinds of α-pyrones and chromene derivatives show interesting biological activities[9,10] and much synthetic effort has been devoted to the synthesis of them.[9,10] We reasoned that we could prepare the chromene skeleton by using the Baylis-Hillman adduct and cyclic β-diketone as depicted in Scheme 1. The reaction of the Baylis-Hillman acetate **1** and cyclohexane-1,3-dione (**2a**) in the presence of K_2CO_3 in DMF gave **3a** in 68% yield. Conversion of **3a** into the corresponding lactone derivative **4a** was conducted by refluxing **3a** in *p*-xylene to give **4a** in 59% yield. The *exo*-double bond of **4a** could be isomerized in its *endo*-position by treatment with DMAP (4,4-dimethylaminopyridine) in refluxing *p*-xylene to give **5a** in 89% yield. As easily expected, the reaction of **3a** in the presence of DMAP in refluxing *p*-xylene gave **5a** in 75% yield directly. In addition, compound **5a** was synthesized directly from the reaction of **1** and **2a** in 78% yield without separation of the intermediate **3a** as also shown in Scheme 1.

As a next trial, we examined the allylic oxidation of **4a** and **5a**, and we found that the reaction of **4a** and PCC (pyridinium chlorochlomate) produced the 3-benzoyl derivative **6a** in 63% yield.[11] However, the oxidation of **5a** with PCC showed no reaction. Like this we found efficient syn-



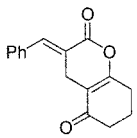
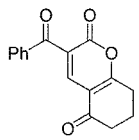
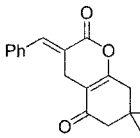
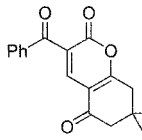
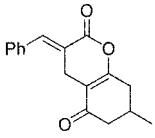
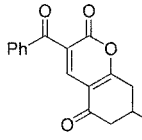
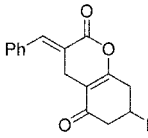
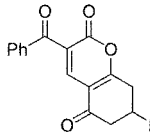
Scheme 1

Table 1. Synthesis of **5a-d** from **1** and **2a-d**[a]

Entry	Substrate	Product **5** (%)
1	 **2a**	 **5a** (78)
2	 **2b**	 **5b** (81)
3	 **2c**	 **5c** (64)
4	 **2d**	 **5d** (81)

[a]Conditions: (i) K_2CO_3 (1.1 equiv), DMF, rt, 1 h, (ii) extractive workup, (iii) DMAP (equiv), *p*-xylene, reflux, 2 h.

Table 2. Synthesis of **6a-d** from **1** and **2a-d**

Entry	Substrate	Intermediate **4** (%)[a]	Product **6** (%)[b]
1	**2a**	 **4a** (59)	 **6a** (63)
2	**2b**	 **4b** (50)	 **6b** (73)
3	**2c**	 **4c** (63)	 **6c** (48)
4	**2d**	 **4d** (59)[c]	 **6d** (31)

[a]Conditions: (i) K_2CO_3 (1.1 equiv), DMF, rt, 1 h, (ii) extractive workup, (iii) *p*-xylene, reflux, 14 h. [b]Conditions: PCC (2.2 equiv), CH_2Cl_2, rt, 24 h. [c]Compound **5d** was formed together (15%).

thetic methods of both 3-benzyl-7,8-dihydro-6*H*-chromene (**5a**) and 3-benzoyl-7,8-dihydro-6*H*-chromene (**6a**).

In order to check the generality of the reaction we used different types of active methylene compounds **2b-d** and obtained similar results as summarized in Table 1 and 2. As shown in Table 1, the use of dimedone (**2b**), 5-methylcyclohexane-1,3-dione (**2c**), and 5-phenylcyclohexane-1,3-dione (**2d**) gave the corresponding 3-benzylchromene derivatives **5b-d** in moderate yields (64-81%) by following the same procedures of Scheme 1. In the same contexts, the corresponding 3-benzoylchromene derivatives **6b-d** were obtained in 31-73% yields analogously by PCC oxidation of **4b-d**.

In summary, we disclosed the synthesis of 3-benzyl-7,8-dihydro-6*H*-chromene and 3-benzoyl-7,8-dihydro-6*H*-chromene derivatives starting from Baylis-Hillman adducts in a practically simple process. The studies on the biological activities of prepared compounds are currently underway.

Experimental Section

Typical procedure for the synthesis of compound 4a: To a stirred solution of the Baylis-Hillman acetate **1** (468 mg, 2.0 mmol) and **2a** (224 mg, 2.0 mmol) in DMF (3 mL) was added K_2CO_3 (304 mg, 2.2 mmol) and strirred at room temperature for 2 h. The reaction mixture was poured into aqueous HCl solution and extracted with ether. After drying with $MgSO_4$, removal of solvent, and column chromatographic purification process (hexanes/EtOAc, 3 : 1) gave pure **3a**, 389 mg (68%). The compound **3a** (286 mg, 1.0 mmol) in *p*-xylene was heated to reflux for 10 h. After removal of solvent and column chromatographic purification process (hexanes/EtOAc, 5 : 1) we obtained pure **4a**, 150 mg (59%). Other compounds **4b-d** were synthesized analogously and the spectroscopic data of **3a**, **4a-d** are as follows.

Compound 3a: 68%; white solid, mp 92-94 °C; IR (KBr) 1712, 1576, 1375, 1273 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.82 (quintet, J = 6.3 Hz, 2H), 2.23 (t, J = 6.3 Hz, 2H), 2.43 (t, J = 6.3 Hz, 2H), 3.51 (s, 2H), 3.86 (s, 3H), 7.32-7.62 (m, 5H), 7.74 (s, 1H), 9.76 (s, 1H).

Compound 4a: 59%; white solid, mp 110-112 °C; IR (KBr) 1741, 1662, 1371, 1165 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.01 (quintet, J = 6.6 Hz, 2H), 2.38 (t, J = 6.6 Hz, 2H), 2.49-2.54 (m, 2H), 3.49-3.52 (m, 2H), 7.30-7.46 (m, 5H), 7.90 (t, J = 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.50, 23.30, 27.24, 36.41, 111.89, 120.84, 128.79, 130.09, 130.74, 134.19, 144.37, 162.40, 165.33, 197.24.

Compound 4b: 50%; white solid, mp 140-142 °C; IR (KBr) 1745, 1664, 1371, 1167 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.12 (s, 6H), 2.32 (s, 2H), 2.45 (t, J = 2.4 Hz, 2H), 3.58-3.61 (m, 2H), 7.40-7.54 (m, 5H), 7.99 (t, J = 2.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 23.19, 28.31, 32.42, 40.99, 50.46, 110.67, 120.85, 128.83, 130.12, 130.78, 134.25, 144.44, 162.60, 163.57, 197.05.

Compound 4c: 63%; white solid, mp 130-133 °C; IR (KBr) 1743, 1660, 1599, 1379, 1165 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.13 (d, J = 6.0 Hz, 3H), 2.09-2.19 (m, 1H), 2.26-2.40 (m, 2H), 2.50-2.63 (m, 2H), 3.58 (s, 2H), 7.40-7.53 (m, 5H), 7.98 (t, J = 2.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.85, 23.30, 28.38, 35.27, 44.75, 111.46, 120.86, 128.82, 130.11, 130.77, 134.24, 144.41, 162.53, 164.67, 197.12.

Compound 4d: 59%; viscous oil; IR (KBr) 1743, 1660, 1165 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.59-2.92 (m, 4H), 3.41-3.56 (m, 1H), 3.63 (s, 2H), 7.22-7.56 (m, 10H), 8.00 (t, J = 2.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ

23.37, 34.81, 38.75, 43.50, 111.75, 120.64, 126.59, 127.32, 128.87, 128.92, 130.21, 130.81, 134.20, 141.82, 144.66, 162.38, 164.38, 196.22.

Typical procedure for the synthesis of 3-benzylchromene derivative 5a: To a stirred solution of the Baylis-Hillman acetate **1** (234 mg, 1.0 mmol) and **2a** (112 mg, 1.0 mmol) in DMF (2 mL) was added K_2CO_3 (152 mg, 1.1 mmol) and stirred at room temperature for 1 h. The reaction mixture was poured into aqueous HCl solution and extracted with ether. After drying with $MgSO_4$ and removal of solvent the crude product was dissolved in *p*-xylene (2 mL). To the reaction mixture DMAP (122 mg, 1.0 mmol) was added and the reaction mixture was heated to reflux for 2 h. After removal of solvent and column chromatographic purification process (hexanes/EtOAc, 3 : 1) we obtained analytically pure **5a**, 191 mg (78%). Other compounds **5b-d** were synthesized analogously and the spectroscopic data of **5a-d** are as follows.

Compound 5a: 78%; viscous oil; IR (KBr) 1734, 1680, 1396 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.12 (quintet, J = 6.6 Hz, 2H), 2.51 (t, J = 6.6 Hz, 2H), 2.82 (t, J = 6.6 Hz, 2H), 3.76 (s, 2H), 7.19-7.34 (m, 5H), 7.54 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.30, 27.72, 36.31, 36.48, 114.62, 126.81, 127.02, 128.66, 129.03, 135.41, 137.42, 161.11, 172.14, 194.05.

Compound 5b: 81%; white solid, mp 139-140 °C; IR (KBr) 1736, 1680, 1396 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.05 (s, 6H), 2.30 (s, 2H), 2.61 (s, 2H), 3.69 (s, 2H), 7.17-7.19 (m, 3H), 7.22-7.25 (m, 2H), 7.44 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.27, 32.65, 36.34, 41.41, 50.45, 113.59, 126.83, 126.87, 128.68, 129.11, 135.15, 137.38, 161.47, 170.80, 193.98.

Compound 5c: 64%; white solid, mp 103-105 °C; IR (KBr) 1736, 1680, 1396 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.15 (d, J = 6.3 Hz, 3H), 2.20 (dd, J = 15.9 and 11.1 Hz, 1H), 2.31-2.41 (m, 1H), 2.50-2.63 (m, 2H), 2.84 (dd, J = 18.3 and 4.5 Hz, 1H), 3.76 (s, 2H), 7.21-7.34 (m, 5H), 7.52 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.82, 28.21, 35.65, 36.33, 44.73, 114.19, 126.83, 126.97, 128.68, 129.07, 135.31, 137.42, 161.24, 171.57, 194.00.

Compound 5d: 81%; white solid, mp 109-110 °C; IR (KBr) 1736, 1680, 1396 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.67-2.87 (m, 2H), 3.05 (d, J = 8.1 Hz, 2H), 3.43-3.53 (m, 1H), 3.78 (s, 2H), 7.22-7.40 (m, 10H), 7.56 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 35.29, 36.39, 38.54, 43.62, 114.36, 126.53, 126.89, 127.33, 127.57, 128.73, 129.04, 129.09, 135.19, 137.34, 141.21, 161.11, 171.13, 193.19.

Typical procedure for the synthesis of 3-benzoylchromene derivative 6a: To a stirred solution of **4a** (254 mg, 1.0 mmol) in CH_2Cl_2 (10 mL) was added PCC (431 mg, 2.2 mmol) and stirred at room temperature for 24 h. The reaction mixture was filtered through a Celite pad and washed thoroughly with CH_2Cl_2. After removal of solvent and column chromatographic purification process (hexanes/EtOAc, 3 : 1) we obtained analytically pure **6a**, 169 mg (63%). Other compounds **6b-d** were synthesized analogously and the spectroscopic data of **6a-d** are as follows.

Compound 6a: 63%; white solid, mp 102-104 °C; IR (KBr) 1753, 1685, 1562, 1390, 1261 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.22 (quintet, J = 6.6 Hz, 2H), 2.62 (t, J = 6.6 Hz, 2H), 2.95 (t, J = 6.6 Hz, 2H), 7.45-7.50 (m, 2H), 7.59-7.64 (m, 1H), 7.79-7.83 (m, 2H), 8.18 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.01, 28.34, 36.42, 114.27, 123.83, 128.61, 129.50, 133.78, 135.92, 141.91, 157.37, 176.87, 190.70, 193.03.

Compound 6b: 73%; white solid, mp 149-151 °C; IR (KBr) 1759, 1684, 1564 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.12 (s, 6H), 2.41 (s, 2H), 2.73 (s, 2H), 7.38-7.43 (m, 2H), 7.52-7.57 (m, 1H), 7.73-7.76 (m, 2H), 8.10 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.31, 32.68, 41.98, 50.39, 113.29, 123.68, 128.63, 129.55, 133.82, 135.91, 141.76, 157.74, 175.65, 190.80, 193.00.

Compound 6c: 48%; white solid, mp 146-147 °C; IR (KBr) 1747, 1684, 1564, 1392, 1263 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.21 (d, J = 6.6 Hz, 3H), 2.30 (dd, J = 16.2 and 11.4 Hz, 1H), 2.40-2.52 (m, 1H), 2.62-2.73 (m, 2H), 2.96 (dd, J = 16.6 and 4.5 Hz, 1H), 7.45-7.50 (m, 2H), 7.58-7.64 (m, 1H), 7.79-7.83 (m, 2H), 8.16 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.79, 28.00, 36.17, 44.64, 113.85, 123.78, 128.61, 129.52, 133.79, 135.92, 141.81, 157.50, 176.30, 190.73, 192.98.

Compound 6d: 31%; white solid, mp 155-157 °C; IR (KBr) 1759, 1685, 1562, 1392, 1252 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.82 (dd, J = 16.8 and 12.0 Hz, 1H), 2.93 (dd, J = 16.8 and 4.5 Hz, 1H), 3.18 (d, J = 8.4 Hz, 2H), 3.53-3.64 (m, 1H), 7.26-7.51 (m, 7H), 7.59-7.65 (m, 1H), 7.81-7.83 (m, 2H), 8.21 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 35.86, 38.27, 43.60, 114.02, 124.08, 126.53, 127.78, 128.66, 129.18, 129.55, 133.88, 135.89, 140.75, 141.68, 157.39, 175.80, 190.66, 192.26.

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