# Synthesis of 3-Benzyl-2-hydroxy-7,8-dihydro-6*H*-quinolin-5-ones from Baylis-Hillman Adducts

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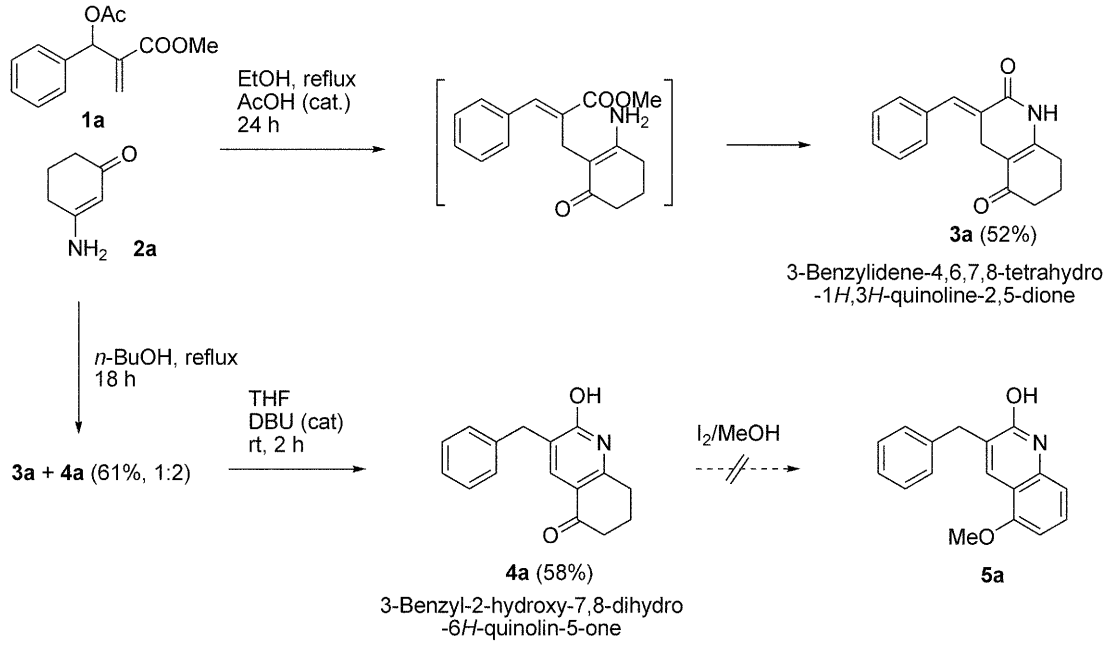
2-Hydroxy-7,8-dihydro-6*H*-quinolin-5-one skeleton is a useful backbone for the synthesis of numerous biologically interesting compounds[1-3] such as carbostyrils (2-hydroxyquinolines)[1b,2a] or huperzine A analogues,[1a] which have shown biological activities including non-steroidal anti-inflammatory activity,[1c] acetylcholinesterase (AChE) inhibitory activity[1a] and antimalarial activity.[1b,2a]

During the studies on the chemical transformation of the Baylis-Hillman adducts toward synthetically useful heterocyclic compounds[4] we envisioned that we could synthesize 3-benzyl-5-methoxycarbostyril derivatives **5**. Our synthetic rationale for **5a** is depicted in Scheme 1. Reaction of the Baylis-Hillman acetate **1** and cyclic enaminone **2**[5] would provide the tetrahydroquinoline-2,5-dione skeleton **3** *via* $S_N2'$ type reaction of cyclic enaminones to the Baylis-Hillman acetates followed by amide bond formation. We thought that the following iodine-assisted oxidative aromatization of cyclohexenone moiety[6] and base-catalyzed isomerization of lactam moiety would afford the desired 3-benzyl-5-methoxycarbostyril derivative **5**.

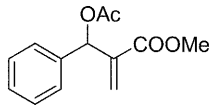
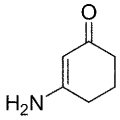
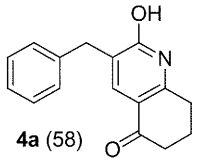
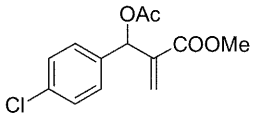
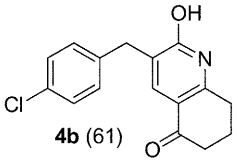
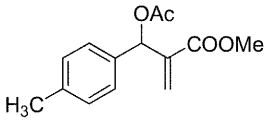
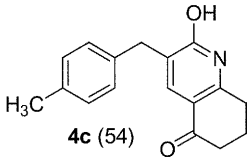
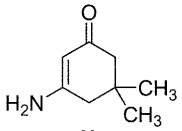
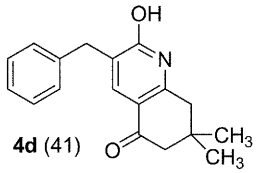
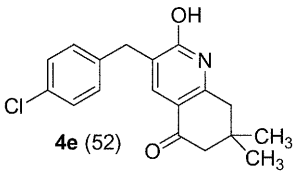
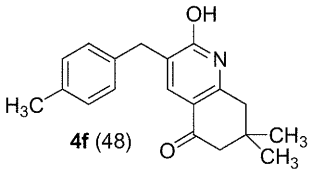
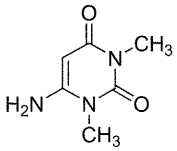
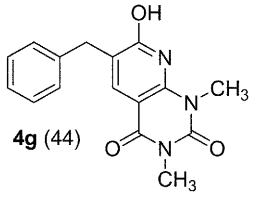
The reaction of Baylis-Hillman acetate **1a** and 3-amino-2-cyclohexenone (**2a**) in refluxing ethanol in the presence of catalytic amount of acetic acid gave 3-benzylidene-4,6,7,8-tetrahydro-1*H*,3*H*-quinoline-2,5-dione (**3a**) as the major product (52%) together with small amounts of **4a** (< 10%). The reaction could also be conducted in *n*-butanol without acetic acid catalyst in a similar pattern. But, when we used *n*-butanol as the solvent, **4a** was observed as the major product on TLC presumably due to the effect of higher reaction temperature than in EtOH. But, **3a** was not changed completely into **4a** even after heating for a long time. Thus we examined the conditions for the effective transformation of **3a** into **4a** and we found a suitable condition fortunately. Conversion of **3a** into **4a** could be carried out easily with catalytic amounts of DBU in THF at room temperature (reflux for the conversion of **3g** into **4g**, entry 7 in Table 1). Thus, we prepared **4a-c** according to the following procedures: reaction of **1a-c** and **2a** in refluxing *n*-BuOH, separation of **3** and **4** as a mixtures, and finally DBU treatment to form **4a-c** as the final products (entries 1-3 in Table 1).

It is interesting to note that the easiness for the conversion



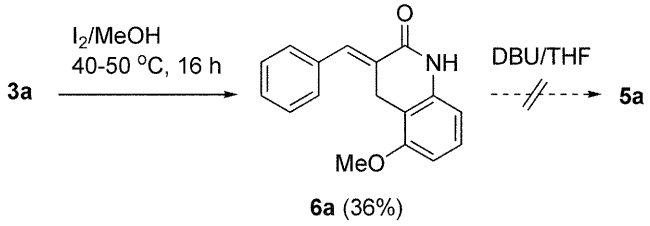

**Scheme 1**

**Table 1**. Synthesis of **4a-g**

| Entry | Substrates | Conditions | Products (%) |
|---|---|---|---|
| 1 |  **1a**  **2a** | 1. *n*-BuOH, reflux, 18 h<br>2. separation of two components together (**3a** + **4a** = 61%)<br>3. THF, DBU (cat), rt, 2 h |  **4a** (58) |
| 2 |  **1b** **2a** | 1. *n*-BuOH, reflux, 26 h<br>2. separation of two components together (**3b** + **4b** = 57%)<br>3. THF, DBU (cat), rt, 2 h |  **4b** (61) |
| 3 |  **1c** **2a** | 1. *n*-BuOH, reflux, 26 h<br>2. separation of two components together (**3c** + **4c** = 58%)<br>3. THF, DBU (cat), rt, 2 h |  **4c** (54) |
| 4 | **1a**  **2b** | *n*-BuOH, reflux, 24 h |  **4d** (41) |
| 5 | **1b** **2b** | *n*-BuOH, reflux, 28 h |  **4e** (52) |
| 6 | **1c** **2b** | *n*-BuOH, reflux, 26 h |  **4f** (48) |
| 7 | **1a**  **2c** | 1. *n*-BuOH, reflux, 28 h<br>2. separation of **3g** (**3g** = 42%)<br>3. THF, DBU (cat), reflux, 9 h |  **4g** (44) |

of the lactam derivatives **3** into **4** was dependent upon the structure of the enaminones **2a-c**. When we used enaminone **2a** (entries 1-3), mixtures of **3** and **4** were produced as mentioned above. Without separation, treatment of the mixtures with catalytic amounts of DBU produced **4**. However, we observed the exclusive formation of **4d-f** without DBU treatment in the reactions of enaminone **2b**, which was derived from dimedone (5,5-dimethyl-1,3-cyclohexanedione, entries 4-6). To the contrary, only the lactam form **3g** was observed for the enaminone **2c** (entry 7). The reason for such different reactivity depending on the structure of enaminones **2a-c** cannot be explained at this stage.

As a next trial, we examined the feasibility for the aromatization reaction of the remaining cyclohexenone moiety of **4a** in order to synthesize 3,5-disubstituted carbostyril derivative eventually. However, unfortunately, all the efforts were found to be ineffective including iodine/MeOH,[6c,6g,6k] iodine/NaOEt/EtOH,[6h,6i] iodine/MeOH/$Hg(OAc)_2$, iodine/$Ce(NH_4)_2(NO_3)_6$/MeOH, or Pd/C in




**Scheme 2**

decaline. It is interesting to note that the aromatization of cyclohexenone moiety of **3a** could be conducted with iodine/MeOH system (40-50 °C, 16 h) to afford **6a** although in low yield (36%).[7] However, the same reaction conditions did not act in the same manner for the transformation of **4a** toward **5a** as noted above. Moreover, the isomerization of **6a** into the desired carbostyril derivative **5a** failed with DBU treatment again, unfortunately (Scheme 2).

In summary, we prepared 3-benzyl-2-hydroxy-7,8-dihydro-6*H*-quinolin-5-one derivatives **4a-f** from the reaction of Baylis-Hillman acetates and cyclic enaminones in moderate yields. Suitable aromatization method of the cyclohexenone moiety in our compounds is currently investigating.

## Experimental Section

**Typical procedure for the synthesis of 4a (Method A):** A stirred solution of the Baylis-Hillman acetate **1a** (700 mg, 3 mmol) and enaminone **2a** (222 mg, 2 mmol) in *n*-butanol (5 mL) was heated to reflux for 18 h. After usual aqueous workup and column chromatographic separation (EtOAc/hexanes, 1 : 1) we obtained a mixture of **3a** and **4a** in 61% isolated yield (310 mg). The mixture of **3a** and **4a** (152 mg, 0.6 mmol) was dissolved in THF (5 mL) and DBU (28 mg, 0.18 mmol) was added and stirred at room temperature for 2 h. After usual aqueous workup and column chromatographic separation (EtOAc/hexanes, 1 : 1) we obtained **4a** in 58% isolated yield (89 mg). The spectroscopic data of **3a**, **3g**, **4a-c**, and **4g** are as follows.

**3a**: white solid, mp 229-232 °C; $^1$H NMR ($CDCl_3$) $\delta$ 2.09 (quintet, $J$ = 6.3 Hz, 2H), 2.42-2.51 (m, 4H), 3.72 (d, $J$ = 2.7 Hz, 2H), 7.35-7.55 (m, 5H), 7.83 (br s, 1H), 7.87 (t, $J$ = 2.7 Hz, 1H); $^{13}$C NMR ($CDCl_3$) $\delta$ 21.32, 24.81, 27.48, 36.55, 110.78, 125.35, 128.68, 129.30, 130.64, 134.86, 139.35, 149.95, 165.64, 195.83.

**3g**: $^1$H NMR ($CDCl_3$) $\delta$ 3.78 (s, 3H), 3.61 (s, 3H), 3.88 (d, $J$ = 2.7 Hz, 2H), 7.39-7.56 (m, 5H), 7.90 (t, $J$ = 2.7 Hz, 1H), 8.87 (br s, 1H).

**4a**: white solid; mp 238-240 °C; $^1$H NMR ($CDCl_3$) $\delta$ 2.11 (quintet, $J$ = 6.3 Hz, 2H), 2.53 (t, $J$ = 6.3 Hz, 2H), 2.81 (t, $J$ = 6.3 Hz, 2H), 3.83 (s, 2H), 7.16-7.28 (m, 5H), 7.85 (s, 1H), 12.80 (br s, 1H); $^{13}$C NMR ($CDCl_3$) $\delta$ 21.44, 26.75, 35.98, 37.15, 114.64, 126.33, 128.38, 129.03, 130.41, 135.73, 139.10, 154.04, 165.32, 194.07.

**4b**: white solid; mp 237-238 °C; $^1$H NMR ($CDCl_3$) $\delta$ 2.12 (quintet, $J$ = 6.3 Hz, 2H), 2.54 (t, $J$ = 6.3 Hz, 2H), 2.77 (t, $J$ = 6.3 Hz, 2H), 3.78 (s, 2H), 7.17-7.26 (m, 4H), 7.85 (s, 1H), 12.85 (br s, 1H); $^{13}$C NMR ($CDCl_3$) $\delta$ 21.38, 26.73, 35.49, 37.11, 114.64, 128.44, 129.78, 130.34, 132.12, 135.89, 137.58, 154.24, 165.24, 194.02.

**4c**: white solid; mp 218-220 °C; $^1$H NMR ($CDCl_3$) $\delta$ 2.11 (quintet, $J$ = 6.3 Hz, 2H), 2.30 (s, 3H), 2.53 (t, $J$ = 6.3 Hz, 2H), 2.82 (t, $J$ = 6.3 Hz, 2H), 3.78 (s, 2H), 7.06 (d, $J$ = 7.8 Hz, 2H), 7.16 (d, $J$ = 7.8 Hz, 2H), 7.83 (s, 1H), 12.90 (br s, 1H); $^{13}$C NMR ($CDCl_3$) $\delta$ 21.00, 21.43, 26.73, 35.48, 37.16, 114.63, 128.90, 129.07, 130.62, 135.55, 135.81, 135.95, 153.99, 165.38, 194.11.

**4g**: white solid; mp 233-235 °C; $^1$H NMR ($CDCl_3$) $\delta$ 3.43 (s, 3H), 3.56 (s, 3H), 3.84 (s, 2H), 7.17-7.31 (m, 5H), 8.03 (s, 1H), 11.49 (br s, 1H); $^{13}$C NMR ($CDCl_3$) $\delta$ 28.46, 29.92, 35.71, 123.37, 126.54, 127.17, 128.56, 128.58, 138.11, 138.80, 146.19, 150.63, 159.95, 164.37.

**Typical procedure for the synthesis of 4d (Method B)**: A stirred solution of the Baylis-Hillman acetate **1a** (700 mg, 3 mmol) and enaminone **2b** (278 mg, 2 mmol) in *n*-butanol (5 mL) was heated to reflux for 24 h. After usual aqueous workup and column chromatographic separation (EtOAc/hexanes, 1 : 1) we obtained **4d** in 41% isolated yield (230 mg). The spectroscopic data of **4d-f** are as follows.

**4d**: white solid; mp 212-214 °C; $^1$H NMR ($CDCl_3$) $\delta$ 1.12 (s, 6H), 2.39 (s, 2H), 2.69 (s, 2H), 3.84 (s, 2H), 7.17-7.31 (m, 5H), 7.84 (s, 1H), 12.87 (br s, 1H); $^{13}$C NMR ($CDCl_3$) $\delta$ 28.25, 33.18, 36.09, 40.28, 50.93, 113.65, 126.36, 128.40, 129.04, 130.17, 135.45, 139.09, 152.60, 165.68, 194.02.

**4e**: white solid; mp 207-208 °C; $^1$H NMR ($CDCl_3$) $\delta$ 1.13 (s, 6H), 2.40 (s, 2H), 2.68 (s, 2H), 3.80 (s, 2H), 7.23 (s, 4H), 7.85 (s, 1H), 13.07 (br s, 1H); $^{13}$C NMR ($CDCl_3$) $\delta$ 28.16, 33.10, 35.53, 40.16, 50.81, 113.60, 128.39, 129.46, 130.30, 132.03, 135.57, 137.52, 152.81, 165.61, 193.94.

**4f**: white solid; mp 188-190 °C; $^1$H NMR ($CDCl_3$) $\delta$ 1.12 (s, 6H), 2.31 (s, 3H), 2.39 (s, 2H), 2.70 (s, 2H), 3.80 (s, 2H), 7.08 (d, $J$ = 7.8 Hz, 2H), 7.18 (d, $J$ = 7.8 Hz, 2H), 7.82 (s, 1H), 12.66 (br s, 1H); $^{13}$C NMR ($CDCl_3$) $\delta$ 28.22, 29.68, 33.19, 35.57, 40.32, 50.93, 113.69, 128.95, 129.13, 130.51, 135.31, 135.84, 135.92, 152.38, 165.62, 194.01.

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7. Spectroscopic data of **6a**: $^{1}$H NMR ($CDCl_3$) $\delta$ 3.77 (s, 3H), 3.96 (d, $J$ = 2.4 Hz, 2H), 6.33 (d, $J$ = 8.1 Hz, 1H), 6.48 (d, $J$ = 8.1 Hz, 1H), 7.06 (t, $J$ = 8.1 Hz, 1H), 7.28-7.47 (m, 5H), 7.83 (t, $J$ = 2.4 Hz, 1H), 7.95 (br s, 1H); $^{13}$C NMR ($CDCl_3$) $\delta$ 25.19, 55.73, 105.05, 107.88, 109.53, 126.48, 128.26, 128.75, 128.89, 130.49, 135.73, 136.91, 137.98, 157.23, 165.40.